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Ophthalmology Times®

CUTTING-EDGE ADVANCEMENTS

July 1, 2019 VOL. 44, NO. 11

CLINICAL DIAGNOSIS | SURGERY | DRUG THERAPY

Xelpros™

(latanoprost ophthalmic emulsion) 0.005%

Take the worry out of coverage with XELPROS Xpress™

Delivers XELPROS™ directly to patients at a low set price

XELPROS IS THE FIRST AND ONLY BAK-FREE FORMULATION OF LATANOPROST—DELIVERED WITH AN INNOVATIVE TECHNOLOGY[1,2]

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INDICATIONS AND USAGE

XELPROS™ (latanoprost ophthalmic emulsion) 0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XELPROS is contraindicated in patients with a known hypersensitivity to latanoprost, or any other ingredients in this product.

Please see Important Safety Information on the back cover and brief summary of Full Prescribing Information inside.

VICTIMS OF EXPLOITATION? Exposing the myth and reality of the physician work ethic

Brief Summary of Prescribing Information for XELPROS™ (latanoprost ophthalmic emulsion) 0.005%, for topical ophthalmic use

XELPROS™ (latanoprost ophthalmic emulsion) 0.005%
See package insert for Full Prescribing Information.

INDICATIONS AND USAGE

XELPROS is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Known hypersensitivity to latanoprost, or any other ingredients in this product.

WARNINGS AND PRECAUTIONS

Pigmentation

XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Eyelash Changes

XELPROS may gradually change eyelashes and vellus hair in the treated eye, including increased length, thickness, pigmentation, and number of lashes. The changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation

XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema

XELPROS should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Herpetic Keratitis

XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses

Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Across multiple clinical trials conducted with XELPROS, the most frequently reported ocular adverse reactions were eye pain/stinging upon instillation and ocular hyperemia, reported in 55% and 41% of patients treated with XELPROS, respectively. Other adverse reactions reported (incidence ≥5%) were conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening. Less than 1% of patients discontinued therapy because of intolerance to the eye pain/stinging or to the ocular hyperemia.

DRUG INTERACTIONS

Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XELPROS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether latanoprost or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XELPROS is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

PATIENT COUNSELING INFORMATION

Potential for Pigmentation

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XELPROS.

Potential for Eyelash Changes

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XELPROS. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated emulsions.

When to Seek Physician Advice

Advise patients that if they develop an intercurrent ocular condition (eg, trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of the multiple-dose container.

Use with Contact Lenses

Advise patients that contact lenses should be removed prior to administration of the emulsion. Lenses may be reinserted 15 minutes following administration of XELPROS.

Use with Other Ophthalmic Drugs

Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

Rx Only

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Cranbury, NJ 08512

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PM-US-XPS-0070 03/2019

SUN OPHTHALMICS

INDICATIONS AND USAGE

XELPROS™ (latanoprost ophthalmic emulsion) 0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XELPROS is contraindicated in patients with a known hypersensitivity to latanoprost, or any other ingredients in this product.

WARNINGS AND PRECAUTIONS

Pigmentation: XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Eyelash Changes: XELPROS may gradually change eyelashes and vellus hair in the treated eye, including increased length, thickness, pigmentation, and number of lashes. The changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema: XELPROS should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Herpetic Keratitis: XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses: Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS

The most common ocular adverse reactions in clinical trials (incidence ≥5%) for XELPROS were eye pain/stinging, ocular hyperemia, conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening.

DRUG INTERACTIONS

Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

Please see brief summary of Full Prescribing Information on the reverse side.

BAK=benzalkonium chloride.

References: 1. XELPROS [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; 2018. **2.** Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.

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CLINICAL DIAGNOSIS | SURGERY | DRUG THERAPY

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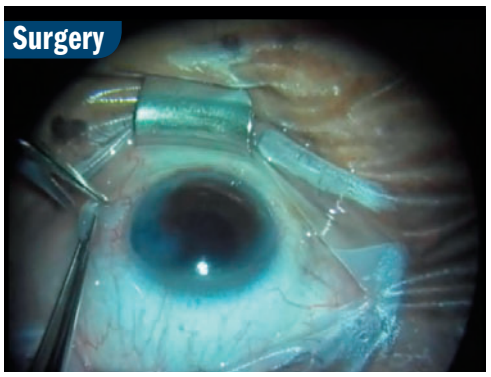


GLAUCOMA SURGEONS SHARE PERSONAL PEARLS FOR TRABECULECTOMY

VARIATIONS in trabeculectomy technique aim to optimize long-term IOP control and minimize the risk of early and late complications. Paul Palmberg, MD, PhD, and Henry D. Jampel, MD, MHS, share elements in their surgical approach that contribute to successful trabeculectomy.

The first consideration is how to avoid bleeding and the need for much cautery, both of which promote scarring, Dr. Palmberg explains.

Highlighting a few steps in his trabeculectomy approach, Dr. Jampel says he initiates the conjunctival peritomy 1.5 to 2 mm posterior to the limbus—a technique he learned from Eugenio Maul Jr., MD—and places a 50/50 mixture of lidocaine and bupivacaine through the snip incision for local subconjunctival anesthesia.

Continues on page 24 : ***Surgical pearls***

Clinical Diagnosis

DREAM EXTENSION STUDY CORROBORATES PRIMARY TRIAL'S CONCLUSION

OPHTHALMOLOGISTS have considered nutritional supplementation with omega-3 fatty acids helpful for dry eye patients and have added them to other treatment modalities. However, high-level evidence for the U.S. population had not been available before the Dry Eye Assessment and Management (DREAM) study.

The DREAM Extension study—adding a second year of treatment—was developed to explore long-term efficacy/safety for dry eye, and to see if any gains over 1 year of omega-3 treatment continued or were lost when its use was discontinued.

"This withdrawal trial is a unique approach in dry eye disease to better understand long-term treatment and its implications," explains Penny A. Asbell, MD, MBA.

Continues on page 30 : ***DREAM***

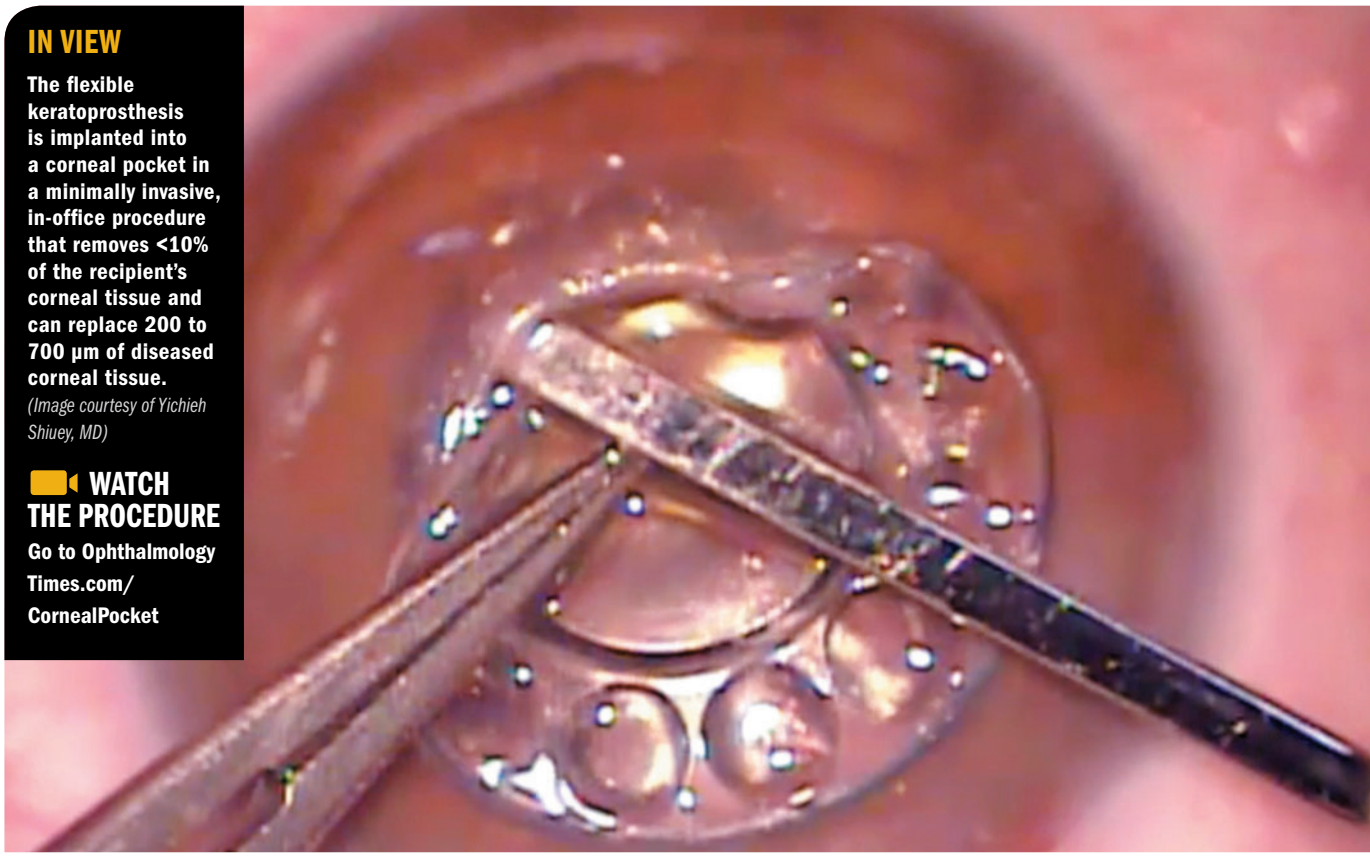
Novel artificial cornea option to transplant

Device in FDA trial for patients with corneal opacity, high risk of penetrating keratoplasty complication

IN VIEW

The flexible keratoprosthesis is implanted into a corneal pocket in a minimally invasive, in-office procedure that removes <10% of the recipient's corneal tissue and can replace 200 to 700 µm of diseased corneal tissue.
(Image courtesy of Yichieh Shiuey, MD)

WATCH THE PROCEDURE
Go to OphthalmologyTimes.com/CornealPocket



By Cheryl Guttman Krader;
Reviewed by Yichieh Shiuey, MD

SCIENCE FICTION may be closer to science fact for an investigational non-penetrating artificial cornea (KeraKlear, KeraMed) as an alternative to penetrating keratoplasty.

The advancement could ultimately help eliminate corneal blindness, said Yichieh Shiuey, MD, practicing cornea and refractive surgeon, Palo Alto Medical Foundation, Sunnyvale, CA, and inventor of the device.

The flexible keratoprosthesis is implanted into a corneal pocket in a straightforward, minimally invasive, in-office procedure that removes <10% of the recipient's corneal tissue and can replace 200 to 700 µm of diseased corneal tissue, explained Dr. Shiuey, founder/president and chief executive officer, KeraMed, Palo Alto, CA.

The artificial cornea has CE mark approval. The device has not received FDA clearance and is currently limited by U.S. law to investigational use only.

Other experience with the device indicates that it has been associated with positive functional outcomes, restoring sight to most patients who were previously blind, and importantly, it has avoided the major complications that are associated with a penetrating keratoprosthesis.

"I was lucky to train as a resident under Claes Dohlman, MD, PhD, who taught me the sad fact that about 98% of

Continues on page 23 : ***Corneal***

VICTIMS OF EXPLOITATION? Exposing the myth and reality of the physician work ethic

ONCE-DAILY
rhopressa®
(netarsudil ophthalmic solution) 0.02%

Achieving IOP control

What makes once-daily Rhopressa® different[1]

- **Consistent IOP reduction up to 5 mmHg** in patients across a range of baseline IOPs
- **Once-daily dosing** to simplify dosing regimens
- **Mild ocular adverse events and no known contraindications** opens up treatment options
- **Unique mechanism of action** for patients who may benefit from improved trabecular aqueous outflow

Rhopressa® is covered for the majority of patients nationwide.[2]

Visit **Rhopressa.com** to learn more about this innovative IOP-lowering treatment.

IOP, intraocular pressure.

INDICATIONS AND USAGE

Rhopressa® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Contact Lenses: Contact lenses should be removed prior to instillation of Rhopressa® and may be inserted 15 minutes following its administration.

ADVERSE REACTIONS

The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa® dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

The corneal verticillata seen in Rhopressa®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes. Most corneal verticillata resolved upon discontinuation of treatment.

Please see brief summary of full Prescribing Information on the adjacent page.

References: 1. Rhopressa Prescribing Information. Irvine, CA: Aerie Pharmaceuticals, Inc; 2017. **2.** MMIT:12/2018.

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aerie® Pharmaceuticals, Inc.

RHOPRESSA® (netarsudil ophthalmic solution) 0.02%
Rx Only

BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

WARNINGS AND PRECAUTIONS
Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been previously contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata
Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

Lactation
There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

aerie®
Pharmaceuticals, Inc.

Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

For more information, go to www.RHOPRESSA.com or call 1-855-AerieRx (1-855-237-4379).

RHOPRESSA is a registered trademark of Aerie Pharmaceuticals, Inc.
U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043

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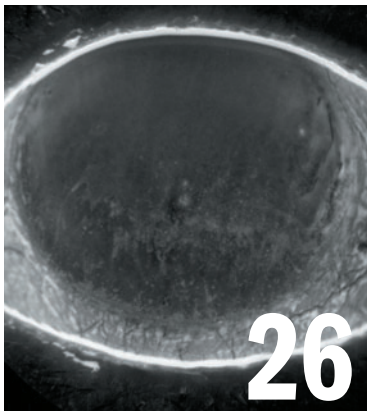

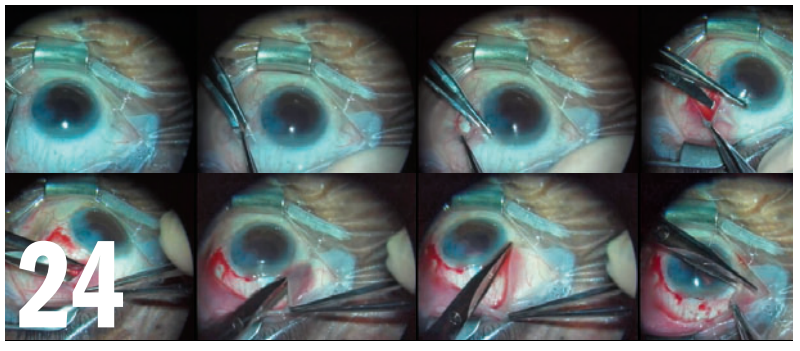

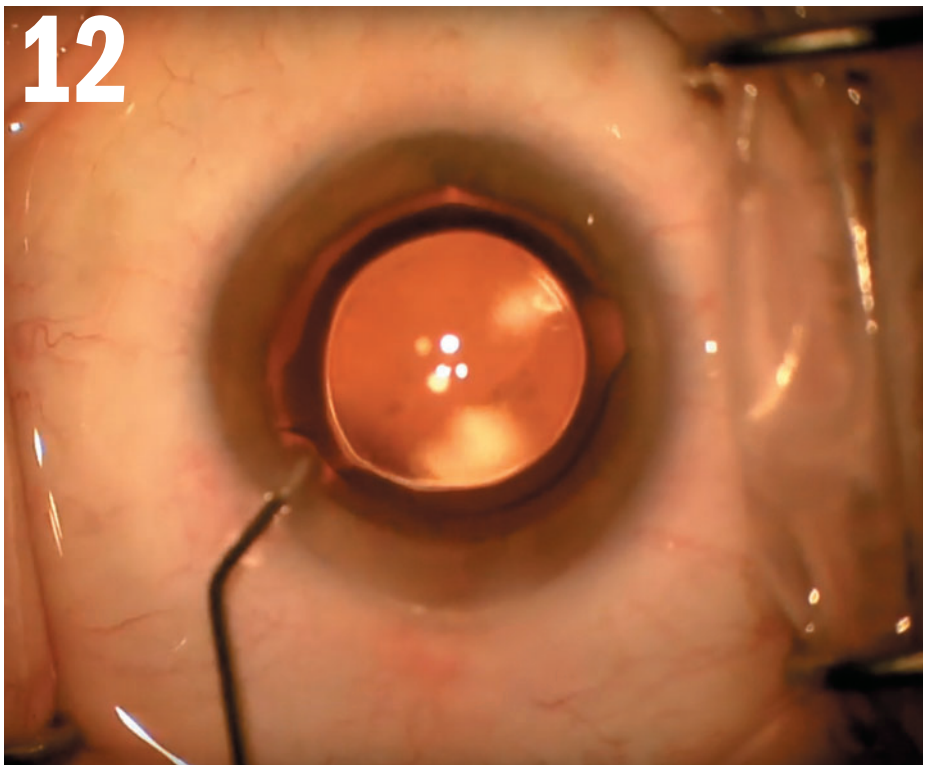

Surgery

Clinical Diagnosis

Drug Therapy

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See what the ophthalmic community is reading on *OphthalmologyTimes.com*

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   http://bit.ly/2ITegs5
2. **Rethinking clinical strategy for treating dry eye disease**
   http://bit.ly/2REbf1A
3. **Keys to integrating, interpreting different types of OCT scans**
   http://bit.ly/2XzwUxk
4. **Tips for successful glaucoma tube shunt surgery**
   http://bit.ly/2ZSOueN

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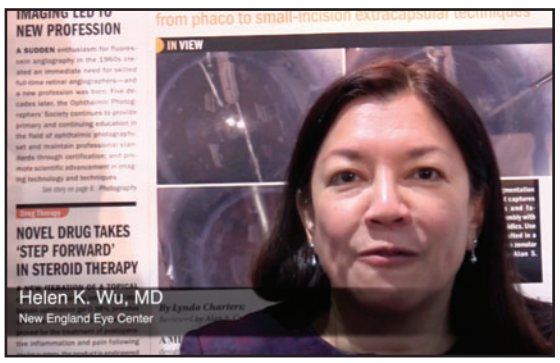

See why Helen K. Wu, MD, calls this lid hygiene device for the treatment of meibomian gland disorder and dry eye disease "an electronic toothbrush" for the eyes.
Watch the interview at http://bit.ly/2wPNBFC

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Through its multifaceted content channels, *Ophthalmology Times* will assist physicians with the tools and knowledge necessary to provide advanced quality patient care in the global world of medicine.

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Truth or myth?

Exposing the reality of the physician work ethic

By Peter J. McDonnell, MD

director of the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, and chief medical editor of *Ophthalmology Times*.

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A RECENT EDITORIAL in *The New York Times*, written by a physician who works at Bellevue Hospital in New York, has seemed to attract a lot of public attention. In "The Business of Health Care Depends on Exploiting Doctors and Nurses," Danielle Ofri, MD, PhD, argues that physicians and nurses are victims.

Dr. Ofri offers some examples:

- **Your elderly patient's son needs to talk to you urgently during your daughter's recital**
- **You work a double shift at the hospital to cover for your colleague who has a family emergency**
- **You have a patient for a 15-minute scheduled visit, but the patient is complex and requires 45 minutes**

According to the editorial, the immediate reaction of doctors and nurses to do the right thing for patients "is being cynically manipulated."

"If doctors and nurses clocked out when the paid hours were finished, the effect on patients would be calamitous. Doctors and nurses know this, which is why they don't shirk. The system knows it, too, and takes advantage."

The author, apparently a primary-care doctor, asserts that these demands on doctors have "escalated relentlessly in the past few decades," patients are sicker today, electronic medical records take too much doctor time, resources are being misallocated, and doctors are burning out.

The article cites a *Harvard Business Review* statistic that for every doctor there are 10 non-doctor workers performing administrative and management duties. The author proposes that at least half of those positions should be given to nurses and doctors: "Heath care is about taking care of patients, not paperwork."

ANOTHER VIEW

My own view is that things aren't quite so bad, and this phenomenon is not quite as new as this article asserts.

My observation growing up was that my father, a general surgeon, never "clocked out," but seemingly worked all the time. Strangers would sometimes come up to me and tell me that my father had saved their lives with a 2 a.m. surgery on a ruptured appendix or a weekend cholecystectomy. Helping people at all hours was what he did, and he loved doing it.

With lower poverty rates and better nutrition today, are Americans really that much sicker today than they were 40 years ago?

There is no question that young physicians can document in electronic medical records much faster than us oldsters. So, allocating some of those non-doctor positions to scribes makes total sense to me.

And the ever-growing federal regulations, expanding compliance requirements and Byzantine demands from insurers related to securing payment for services translate into an ever-growing need for workers who will never touch patients because they are busy generating reports and appealing denials for payment.

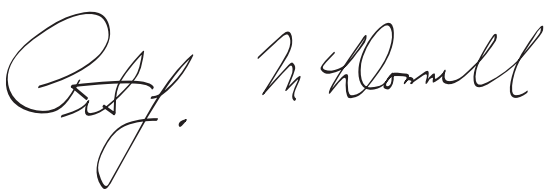
PATIENTS' NEEDS TOP PRIORITY

While missing a child's recital or sporting event is disappointing, our children will understand and forgive (as my father's non-attendance at most of our games was a non-issue for me and my sisters).

It is because most Americans believe their doctors and nurses will make their patients' needs the top priority that we are held in such high regard by the public. For this same reason, we are compensated extremely well compared with the vast majority of our fellow Americans, earning more than we have the time to spend.

Is there an opportunity to better allocate tasks and reduce administrative and regulatory burdens on physicians and nurses so that they can spend more time touching and caring for their patients? Sure.

Are we physicians (or at least we ophthalmologists) and nurses victims of exploitation? Not even close in my view. ■



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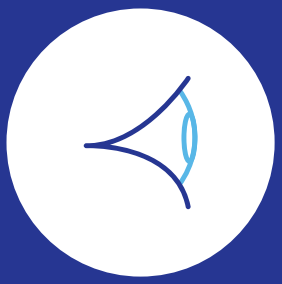
- *https://hbr.org/2013/09/the-downside-of-health-care-job-growth*

THE CYCLE OF INFLAMMATION IN DRY EYE DISEASE[2]



Ocular Surface Stress

Inflammation

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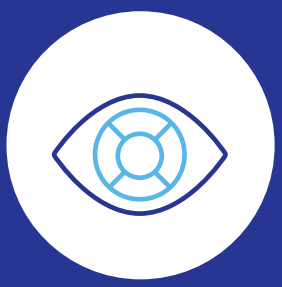

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To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

References:
1. Xiidra [Prescribing Information]. Lexington, MA: Shire US. **2.** TFOS DEWS II Research Subcommittee. Report of the Research Subcommittee of the Tear Film & Ocular Surface Society Dry Eye WorkShop II (2017). *Ocul Surf.* 2017;15(3):269-275.

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CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg / day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.
Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.
Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

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Teleglaucoma in the community: Taking it to the neighborhood

Established in other areas, telemedicine implementation slow in glaucoma treatment

By Nancy Groves; *Reviewed by Lindsay Anne Rhodes, MD*

Traditional in-office glaucoma screening and treatment approaches fail to reach many patients in the population, resulting in an increase of significant visual deterioration or even blindness. Community models that provide accessible, convenient, and efficient care to high-risk populations could be part of the solution, said Lindsay Anne Rhodes, MD, assistant professor, Department of Ophthalmology and Visual Sciences, University of Alabama at Birmingham.

"If we can make it easier and more convenient for patients to get to their appointments and have regular checks, maybe we will do a better job of finding them before their condition gets worse," said Dr. Rhodes, who is participating in one teleglaucoma initiative, known as EQUALITY (Eye Care Quality and Accessibility Improvement in the Community).

IMPLEMENTATION SLOW

Telemedicine is well established in the diagnosis of diabetic retinopathy and retinopathy of prematurity, but implementation has been slower for glaucoma, she said. Reasons include the need for a combination of structural and functional testing, often conducted with sophisticated, expensive instruments, and challenges such as image readability, and follow-up adherence.

A community model holds promise for improving the management of glaucoma, particularly in small towns, rural areas, and inner cities where specialized medical services are often limited or nonexistent.

> 'If we can isolate high-risk populations based on age, race, and family history of glaucoma, it improves our ability to find and treat glaucoma.' - *Lindsay Anne Rhodes, MD*

Goals include providing accessible, convenient, and efficient care; using improved imaging and diagnostic modalities (portable fundus cameras, smartphone cameras, tablet- or virtual reality-based visual field testing, and spectral-domain optical coherence tomography); increasing rates of diagnosed and treated glaucoma; and allowing glaucoma specialists to focus on advanced disease and surgical work.

PROJECTS BEING TESTED

Teleglaucoma projects are being tested in a number of areas, most falling into either of two categories. One is population-based detection targeting high-risk populations.

"Checking everybody for glaucoma is not a good way of finding the disease," Dr. Rhodes explained. "If we can isolate high-risk populations based on age, race, and family history of glaucoma, it improves our ability to find and treat glaucoma."

In this model, screening can take place in numerous types of locations such as primarycare settings, federally qualified health centers, Veterans Administration clinics, retail locations, rural areas, and community centers or churches.

Some screening projects reach out to at-risk urban communities, partnering with community organizations to provide eye exams on mobile units, offer treatment on-site, and arrange follow-up care.

One example of this approach is TECS (Technology-Based Eye Care Services), funded primarily by the Department of Veterans Affairs.

Nearly 39% of the patients screened received a glaucoma-related diagnosis, as reported in a 2017 study, which is far higher than the prevalence of glaucoma in the general population, Dr. Rhodes noted.

Another approach is the vertically integrated network. This approach taps into a network of primary eye care providers such as optometrists—more likely to be found in small towns, rural areas, or underserved urban communities than glaucoma specialists—to perform comprehensive dilated eye exams.

Optical coherence tomography image, visual field tests, and optic nerve head photography are then sent to a reading center for remote subspecialist review.

The EQUALITY project, in which screening and follow-up take place in retail-based, primary-care settings serving communities with a large percentage of African Americans, follows this particular model.

Walmart Vision Centers were chosen as partners for the EQUALITY program because in the rural areas of Alabama, where the project is based, Walmart stores are often the largest, or only, retail centers and therefore provide a convenient central point of access for the target population, Dr. Rhodes explained.

Since the screenings are conducted at a regularly staffed clinic, patients know that they can readily return for follow-up visits, while the optometrists can bill for their services, making the project more sustainable.

In a 2016 study conducted at two EQUALITY sites, Dr. Rhodes reported that a total of 56% of the patients screened had a glaucoma-related diagnosis.

Based on a review of teleglaucoma programs, the keys to success that Dr. Rhodes has identified include targeting high-risk populations; choosing imaging modalities based on budget, convenience, and portability; engaging community partners to spread awareness and increase attendance; and utilizing patient navigators, social workers, and technology to increase follow-up adherence rates.

TAKE-HOME

- ***Improved knowledge about glaucoma and a high intent to pursue eye care may lead to improved detection of early disease, thus lowering the risk of blindness among patients.***

TELEGLAUCOMA OUTLOOK

Future directions that could enhance the success of teleglaucoma include comparisons of emerging imaging devices such as smartphone cameras and tablets and application of artificial intelligence in the reading of optic nerve photos.

Additional research on effectiveness and cost-effectiveness is also needed to improve reimbursement rates. ■

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This article is adapted from Dr. Rhodes' presentation at the American Glaucoma Society 2019 annual meeting. Dr. Rhodes has received funding and support for the EQUALITY project from the Centers for Disease Control and Prevention, Research to Prevent Blindness, EyeSight Foundation, Carl Zeiss Meditec, and Heidelberg Engineering.

Reimbursement remains hurdle for teleglaucoma in United States

Capitated health-care models may be best positioned to take advantage of telehealth

By Conni Bergmann Koury; *Reviewed by Siddarth Rathi, MD, MBA*

WORLDWIDE, HEALTH-CARE systems are implementing models of teleglaucoma care. Clarifying reimbursement considerations, however, is necessary for greater strides toward U.S. adoption, according to Siddarth Rathi, MD, MBA, assistant professor of ophthalmology at NYU Department of Ophthalmology.

Dr. Rathi noted some examples for consideration.

CANADA

The University of Alberta's teleglaucoma program consists of a remote or in-house pathway, he noted. Patients on the remote pathway visit a local ophthalmologist or optometrist who collects standardized history, examination, and imaging findings. The eye-care provider securely transmits the information to a remote glaucoma specialist who delivers an electronic recommendation to the referring clinician. The in-house program is a tertiary0care referral center in Edmonton.

These individuals see an ophthalmic technician who obtains the history, exam, and imaging, according to Dr. Rathi. A glaucoma specialist reviews the data and sends a report to the referring provider.

The program seeks to reduce the time patients spend in the clinic, and wait to have a glaucoma evaluation. In Canada, Medicare reimburses at two-thirds of the conventional in-person fee for these consultations.

AUSTRALIA

At the Lions Outback Vision Center in Australia, the patient sees a local optometrist who sends the history, exam findings, and imaging to the remote ophthalmologist. Dr. Rathi said that the specialist videoconferences with the patient and the local provider to deliver the recommendations.

Australia Medicare reimburses clinicians if there is a live audio-video component to the encounter and the patient is located at least 15 kilometers away from the consulting ophthalmologist or resides in a care facility for indigenous Australians.

"Initially, there was no reimbursement for the local referring optometrist," Dr. Rathi said, "After Medicare implemented reimbursement covering technical costs for the referring physician, the program had a 3.5-fold increase in utilization during the next 12 months."

WHAT ABOUT THE UNITED STATES?

Given the mix of fee-for-service and capitated care health-care delivery models in the United States, as well as the evolution of telehealth reimbursement, a combination of teleglaucoma models could be sustainable, according to Dr. Rathi.

"For example, glaucoma care could be provided via synchronized consultation with the patient who is at home or in the primary-care physician's office," he said. "In the future, dedicated telehealth centers could have locations across the country."

Dr. Rathi noted that like the Canadian version, asynchronized consultations could be useful where the optometrist or general ophthalmologist routes the clinical information to an off-site specialist for collaboration.

"Remote monitoring of glaucoma patients could include home-based IOP measurements and virtual reality visual field exams," he said.

REIMBURSEMENT

These remote glaucoma management models have unique advantages, but adoption of telehealth services is often determined by reimbursement. In the United States, a direct-to-consumer model where patients pay for telehealth services is not well-suited to glaucoma.

"Within a capitated healthcare system on the other hand, resources can more readily be dedicated toward creating the needed infrastructure," according to Dr. Rathi.

Reading centers with peer-to-peer consultation networks would allow high-risk patients to be prioritized for in-person glaucoma clinic visits, while low-risk patients could be followed remotely.

Fee-for-service is the predominant payment model in the United States.

MEDICARE

Medicare reimburses for telehealth if strict requirements are met. First, the patient must be physically located in a rural area—there is no coverage for patients in urban or suburban settings. Second, the patient must be located in a health-care facility (i.e., critical access hospital, rural clinic, or a physician's office).

The home setting is not included. The interaction must be over live two-way audio/video communication. The physician must be physically located in the United States. If these requirements are met, payment is on par with in-person fees using standard remote patient monitoring codes with modifier 95 for synchronized telemedicine. Medicare covers asynchronized telemedicine only in Alaska and Hawaii, under active telemedicine demonstration programs (primarily for diabetic retinopathy screening).

"This year's much-awaited Medicare telehealth policy updates included now covering remote consultation and pre-recorded patient information where a physician can evaluate a video or image with an established patient and offer interpretation within 24 hours," Dr. Rathi explained. "Now, virtual check-ins with audio and medical discussions are reimbursable without rural location requirements. Medicare provides coverage for remote physiologic monitoring for chronic disease—IOP may fall into this category. It is important to note that this is new territory for ophthalmology and is evolving, and the specialty has no prior experience with these codes."

COMMERCIAL INSURANCE

Coverage by commercial carriers is often dictated by state. Some states have passed telemedicine parity laws that mandate commercial insurers extend telemedicine coverage for any covered in-person service. Although a positive development, most of these laws do not mandate payment parity. A carrier can have large differences in its reimbursement rates for services rendered in telemedicine compared with in-person services, possibly disincentivizing physicians from providing these services.

Physician medical licensure requiring physicians to be licensed in the state where the patient is physically located has been a regulatory barrier to telehealth adoption. In 2017, the Interstate Medical Licensure Compact allowed expedited licensure in party states.

CONCLUSION

"Reimbursement for telehealth initiatives is far from guaranteed, with capitated systems likely leading the way in initial teleglaucoma applications," Dr. Rathi noted. As shown in Australia, reimbursement leads to increased adoption of telemedicine and virtual consultation. Telemedicine parity laws are helping to move efforts forward as Medicare coverage of telehealth is evolving. ■

TAKE-HOME

- ***Reimbursement for telehealth initiatives remains an uncertainty in the United States today, with capitated systems at the forefront in initial teleglaucoma applications.***

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This article was adapted from Dr. Rathi's presentation at the 2019 American Glaucoma Society annual meeting. He has no financial interest in any aspect of this report.

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Ophthalmology Times 2nd PLACE RESEARCH SCHOLAR HONOREE

How does diabetic retinopathy influence cataract surgery?

Study compares preoperative risk factors, co-pathology in patients

By John R. Chancellor, MD, MS; Mohamed K. Soliman, MD, MSc; Joseph Levy, MD, PhD; Mohammed Elfaramawi, MD, PhD, MPH, MSc ; Ahmed B. Sallam, MD, PhD; *Special to* Ophthalmology Times

EDITOR'S NOTE

Ophthalmology Times is pleased to recognize John R. Chancellor, MD, MS, resident, Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, AR, as the second-place honoree of the second Ophthalmology Times Research Scholar Honoree Program. Dr. Chancellor's abstract is featured here. The Ophthalmology Times Research Scholar Honoree Program is dedicated to the education of retina fellows and residents by providing a unique opportunity for fellows/residents to share notable research and challenging cases with their peers and mentors. The program is supported by unrestricted grants from Regeneron Pharmaceuticals and Carl Zeiss Meditec Inc. Look for more case study honorees in upcoming issues of Ophthalmology Times.

PURPOSE

At some point, every ophthalmologist is going to have a diabetic patient walk into the office who is going to have a visually significant cataract.

Diabetic retinopathy is the leading cause of vision loss among patients with diabetes and a primary cause of blindness among working-age adults.

As a result, the purpose of the study was to evaluate how diabetic retinopathy influences cataract surgery.

The primary aims included studying preoperative risk factors, intraoperative complications, and postoperative outcomes.

METHODS

The study examined a retrospective clinical database study of 217,107 eyes that underwent cataract surgery at eight UK National Health Service hospitals between 2000-2015. Of those eyes included in the database study, 138,100 were not diabetic; 41,059 were diabetic; and for the remaining 37,948, the diabetic status was not recorded.

Our methods for the evaluation of risk factors compared prevalence of preoperative risk factors and co-pathology between diabetic patients and non-diabetic patients.

In the evaluation of complications, we compared incidences of intraoperative complications between diabetic patients and non-diabetic patients during cataract surgery.

Lastly, we compared postoperative outcomes between diabetic patients and non-diabetic patients after cataract surgery.

Our methodology included strict inclusion criteria, including no co-pathology, except amblyopia; no simultaneous surgical procedures, except intraocular injection; and clear ETDRS grading of retinopathy was required.

RESULTS

In examining preoperative risk factors, we found that epiretinal membranes (ERM), small pupil, and brunescent/white cataract are more common in diabetics.

Our review of intraoperative complications found that posterior capsular rupture, dropped nuclear fragment, corneal edema, and overall complication rates were higher among diabetic patients.

In our examination of postoperative outcomes, we found that visual acuity, good vision (≤20/40), and pseudophakic cystoid macular edema (CME) were negatively associated with diabetes and degree of diabetic retinopathy. The effect of preoperative diabetic macular edema (DME) on visual acuity and good vision was similar to the effect of having moderate non-proliferative diabetic retinopathy (NPDR).

As we evaluated outcomes, we looked at the difference in preoperative and postoperative visual acuity between the diabetic and non-diabetic patients.

Using logistic regression analysis for pre- and postop (four to 12 weeks) BCVA > logMAR 0.3 with 95% CI, we examined the chance of having poor vision postoperatively.

We examined the chance of having pseudophakic cystoid macular edema postoperatively, using logistic regression analysis for postop CME with 95% CI.

We also wanted to determine if we could predict postoperative vision based on preoperative vision and diabetic status. We utilized a linear regression model for age, preop DME, diabetic status, preop visual acuity, and postop visual acuity at four to 12 weeks with 95% CI.

There also are some limitations that we acknowledge, including retrospective design, missing short-term follow up data, and missing details of grading of cataract type/density.

We found that diabetics are seeing worse, they are having poor vision and are developing more macular edema after surgery. The worse their retinopathy, the worse their outcome.

CONCLUSION

This study provides data to assist in the planning of cataract surgery and providing informed consent in diabetic patients.

It would be reasonable to recommend performing cataract extraction on diabetic patients early, before the development of significant retinopathy or vision decline. ■

VIEW PRESENTATION ONLINE

VIDEO See Dr. Chancellor's presentation of diabetic retinopathy's influence cataract surgery:
www.ophthalmologytimes.com/chancellor-presentation

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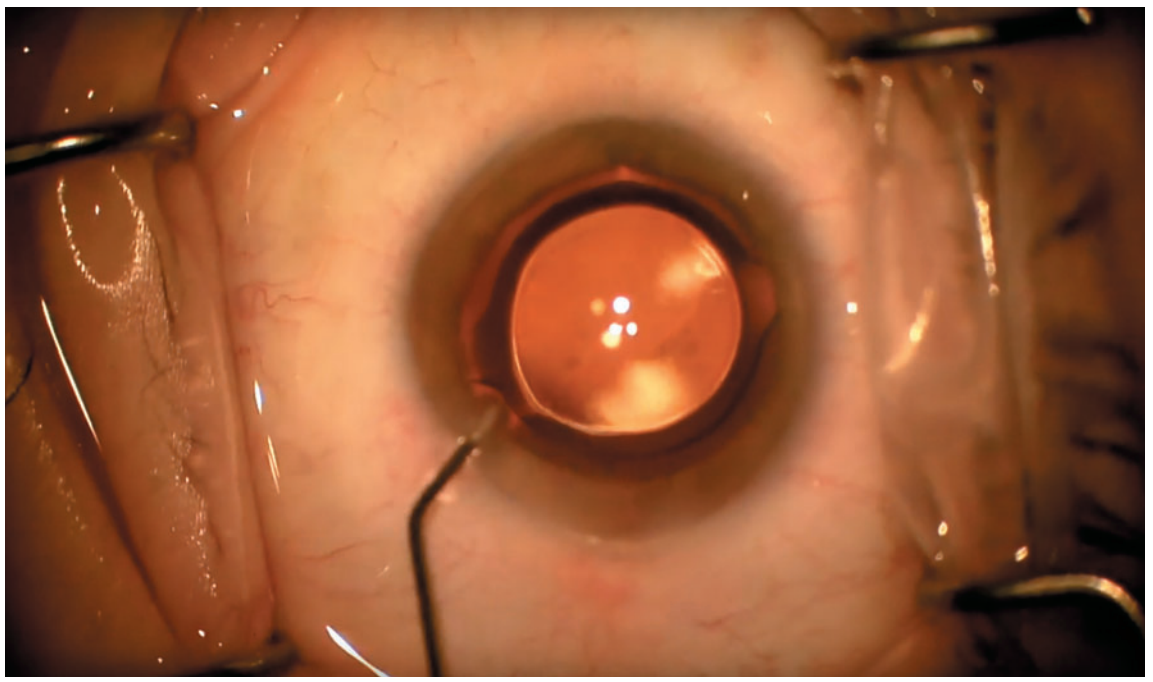
Dr. Chancellor has no financial interests or relationships to disclose. None of the listed participants on his project have any financial interests or relationships to disclose.



Immediate IOP adjustments with tonometry can help physicians reduce the risk of cystoid macular edema in patients. *(Image courtesy of John S. Jarstad, MD)*

TONOMETRY CAN SERVE AS TOOL IN CME PREVENTION

Research offers guidance on NSAID use, identifies etiologic role of abnormal IOP

By Cheryl Guttman Krader; *Reviewed by John S. Jarstad, MD*

take-home

- ***Research studies find that normalization of IOP at the end of cataract surgery can reduce the risk of cystoid macular edema and mitigate the need for adjunctive perioperative NSAID treatment in routine cases involving patients without diabetes.***

The use of tonometry to check and guide adjustment of IOP immediately at the end of cataract surgery can reduce the risk of cystoid macular edema (CME). After that, patients can receive a topical corticosteroid postoperatively; perioperative nonsteroidal anti-inflammatory drug (NSAID) use may not be essential in routine cases.

Adjunctive NSAID treatment, however, is essential to reduce the risk of CME in all patients with diabetes and is also recommended in any case where there is an intraoperative complication or other risk factor for CME, said John S. Jarstad, MD.

Dr. Jarstad's comments were based on studies conducted at the Department of Ophthalmology, University of Missouri School of Medicine, Columbia, where he is associate professor of clinical ophthalmology and director of cataract and refractive surgery.

Dr. Jarstad

"Our study looking at the effect of NSAIDs on CME is the largest study to date on this topic, but it is retrospective," he said. "The findings on omitting NSAIDs in routine cases if IOP is accurately assessed and adjusted into the normal range in the operating room should be investigated in a future controlled randomized trial."

The incidence of CME in eyes operated on without perioperative NSAID use was investigated in a single surgeon retrospective study conducted by Dr. Jarstad as primary surgeon with the collaboration of Van Nguyen, MD, ophthalmology resident, and Carli Wittgrove, medical student. The study included data from 930 eyes that underwent femtosecond laser-assisted cataract surgery (FLACS) or microincisional cataract surgery (MICS) between July 2016 and January 2018.

"The period chosen for the study was a time when we were not using perioperative NSAIDs because of a supply shortage," Dr. Jarstad explained. "Rick Fraunfelder, MD, department chairman, suggested we review patients' outcomes to investigate his impression that NSAIDs were not needed to prevent CME in routine cases."

In all cases, IOP was checked and adjusted with BSS to between 16 mm Hg and 21 mm Hg using a sterile 27-gauge cannula with a Tono-Pen (AO Reichert) and sterile cover immediately after completion of surgery while the patient was still on the operating table. Patients whose visual acuity did not correct to 20/20 during follow-up were evaluated over the next several weeks with optical coherence tomography (OCT) of the macula to detect CME.

CME was diagnosed by imaging in two eyes (8%) of 25 patients with diabetes but in only 13 eyes (1.4%) eyes of 905 patients without diabetes, he said.

"A Cochrane analysis including 948 eyes from 6 studies reported that the incidence of CME ranged from 1.2% to 4%," he said. "Our study results fall within this incidence range, providing evidence that NSAIDs may not be essential to prevent CME in routine cases in non-diabetic patients if IOP is adjusted immediately after surgery."

IOP AS A CME RISK FACTOR

The value of checking IOP with tonometry and adjusting it to between 16 and 21 mm Hg was shown a previous study published by Dr. Jarstad and colleagues [Jarstad JS, et al. *Korean J Ophthalmol.* 2017;31:39-43], which included 176 consecutive eyes that underwent FLACS or MICS.

Continues on page 14 : ***Tonometry***

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Special Report) LEADING-EDGE RESEARCH IN **ANTIBIOTIC AND ANTI-INFLAMMATORY DRUGS**

Clinical trial suggests safety of unpreserved levofloxacin

Intracameral injection of cefuroxime, moxifloxacin decrease risk of endophthalmitis

By Cheryl Guttman Krader; *Reviewed by Harvey S. Uy, MD*

RESULTS OF A prospective, double-masked, randomly selected comparative trial suggest that intracameral unpreserved levofloxacin 0.5% (Oftaquix, Santen) is a viable option for prophylaxis of endophthalmitis after cataract surgery, said Harvey S. Uy, MD.

Dr. Uy

The study included 114 eyes that received intracameral injection of unpreserved levofloxacin 0.5 mg/0.1 mL or unpreserved moxifloxacin 0.5 mg/0.1 mL (Vigamox, Alcon Laboratories) after uncomplicated cataract surgery with IOL implantation.

There were no statistically significant differences between study groups in the outcomes analyses that considered various safety endpoints, said Dr. Uy, clinical associate professor of ophthalmology, University of the Philippines, and medical director, Peregrine Eye and Laser Institute in Makati, Philippines.

"There is growing evidence that intracameral injection of cefuroxime and moxifloxacin decrease the risk of endophthalmitis after cataract surgery," he said. "The use of these antibiotics may be limited in certain situations, and so there is a need for alternatives that may be more widely accessible."

Dr. Uy noted that while the study was not powered to show a difference in efficacy between moxifloxacin and levofloxacin for preventing endophthalmitis, "the results indicate that the two fluoroquinolones are equally safe when used as antibacterial prophylaxis after cataract surgery."

Patients were randomly selected 1:1 into two groups. In each case, the antibiotic was withdrawn in the operating room from the commercially available multidose bottle containing product marketed for topical ophthalmic use.

Postoperatively, patients received the same medication regimen, which consisted of topical prednisolone acetate 1% and topical gatifloxacin. They returned for follow-up after one day, seven days, and 30 days.

Researchers used coherence tomography imaging to measure central subfield retinal thickness and macular volume, specular microscopy to measure endothelial cell density, and pachymetry to measure central corneal thickness prior to surgery and at postoperative visits. Changes from baseline at each follow-up visit were compared between the groups.

The patients receiving moxifloxacin and levofloxacin were well-matched in their baseline age and clinical characteristics, including cataract density. There were no statistically significant differences between the study groups in any of the outcome measures at any timepoint after surgery.

"There were also no significant adverse events in either study group, and no patient developed endophthalmitis or toxic anterior segment syndrome," Dr. Uy noted. "Corneal edema was the most common adverse event and occurred similarly in both groups."

Vancomycin has also been injected intracamerally to prevent endophthalmitis, Dr. Uy concluded. Reports of hemorrhagic occlusive retinal vasculitis limit the use of vancomycin for infection prophylaxis. ■

TAKE-HOME

- ***A clinical trial suggests that intracameral unpreserved levofloxacin 0.5% is a viable option for prophylaxis of endophthalmitis after cataract surgery.***

HARVEY S. UY, MD

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This article was adapted from Dr. Uy's presentation at the 2019 meeting of the American Society of Cataract and Refractive Surgery. Santen provided research funding for the study. Dr. Uy has no other relevant financial interests to disclose.

TONOMETRY

(Continued from page 12)

The study was conducted to assess the accuracy of IOP determination by palpation and had an unexpected finding that abnormal immediate postoperative IOP was a cause of CME in routine cataract surgery.

Cases were performed by two cataract surgeons and four senior residents. IOP was estimated at the end of surgery by "feel," and after the value was recorded, IOP was measured with a sterile handheld Barraquer surgical tonometer and a Tono-Pen. IOP was adjusted on the table if the Tono-Pen reading was ≥30 mm Hg or <10 mm Hg. Data showed good agreement between the two instrument measurements.

There were, however, large differences comparing the palpated IOP values with tonometry data. Immediate postoperative IOP thought to be safe (10 to 30 mm Hg) when estimated by surgeons' feel ranged from 9 to 67 mm Hg when verified with tonometry.

Dr. Jarstad noted that when the paper was submitted, one of the reviewers commented that experienced surgeons can tell what the IOP is by feel.

"Our study refutes that belief," he said. "I have done over 25,000 cataract cases, and in the study I did no better than my residents at accurately judging IOP."

DIVING DEEPER

Researchers did find that the ability to predict IOP accurately by palpation improves when practicing immediate verification with tonometry and by using a quick "double tap" through the side-port incision if IOP is too high.

An analysis investigating the idea that abnormal IOP is a CME risk factor found that compared with eyes with an adjusted IOP between 16 mm Hg and 21 mm Hg, eyes with an IOP <16 mm Hg had a fourfold greater incidence of CME and those with an IOP >21 mm Hg had a 2.5-fold greater risk. The study also indicated normalizing IOP at the conclusion of surgery can help prevent postoperative IOP spikes, the most common complication after cataract surgery.

The study found there was a <5 mm Hg average IOP change comparing the immediate postoperative value to the measurement obtained in the clinic on the first postoperative day.

The opportunity for cost savings by checking IOP in the OR was indicated by data showing that as many as 33% of postoperative patients without IOP adjustment in the OR required an adjustment on the first day after surgery compared with just 5% of patients whose IOP was adjusted immediately after surgery. ■

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Special Report) LEADING-EDGE RESEARCH IN **ANTIBIOTIC AND ANTI-INFLAMMATORY DRUGS**

Controlled trial identifies limited benefits of adjunctive NSAIDs

Research does not support routine use to decrease the risk of PCME

By Cheryl Guttman Krader; *Reviewed by Sean J. McCafferty, MD*

RESULTS OF A large prospective, randomly selected trial provide insight on the benefits and role of adjunctive topical nonsteroidal anti-inflammatory drug (NSAID) use in the postoperative medication regimen for patients undergoing cataract surgery.

Without industry support, Sean J. McCafferty, MD, and colleagues at Arizona Eye Consultants, Tucson, undertook the ambitious Arizona Surgical Eye Study (ASES).

Outcomes showed that the addition of a topical NSAID to a corticosteroid after cataract surgery significantly reduced the incidence of pain and inflammation at one and six weeks after cataract surgery.

LIMITED BENEFIT

A benefit for preventing pseudophakic cystoid macular edema (PCME) was seen only in patients with risk factors for that complication. There were no differences between patients who used the combination treatment versus a corticosteroid alone with respect to macular edema, endothelial cell loss, BCVA outcomes, capsular phimosis, or two- and four-year YAG capsulotomy rates, said Dr. McCafferty, founder, Arizona Eye Consultants, and clinical assistant professor, University of Arizona College of Medicine and College of Optical Science, Tucson.

"A survey conducted prior to designing the study showed that the primary reason most cataract surgeons were prescribing a topical NSAID was to reduce the risk of PCME, which is off-label use," he said. "These medications are indicated for decreasing postoperative inflammation and pain, but they have also been touted for decreasing posterior capsule opacification, capsular phimosis, and endothelial cell loss."

Dr. McCafferty noted that adding a topical NSAID to corticosteroid treatment after cataract surgery adds cost and can cause discomfort for patients.

"Whether it brings any real benefit for these off-label uses has been a nagging question," he said. "Results of our study confirm its efficacy for decreasing inflammation and pain, but do not support its routine use to decrease the risk of PCME or for any other of the described reasons."

Dr. McCafferty said that, based on the findings of the ASES, he is routinely prescribing a topical NSAID for postoperative use only for patients who have one of the PCME risk factors that was identified in the trial.

The ASES included 1000 eyes that were randomized to blinded treatment with placebo or nepafenac 0.3% (Ilevro, Alcon Laboratories) once daily for four weeks.

"A very large sample size was needed to identify differences between treatment groups for the various endpoints," Dr. McCafferty explained. "The study was designed to evaluate a single NSAID product to avoid having multiple arms and an even larger population."

take-home

- ***A randomized trial found adding a topical NSAID to a topical corticosteroid reduced pain and inflammation compared with corticosteroid treatment alone. A benefit for reducing cystoid macular edema was seen only in at-risk patients.***

OUTCOMES

Postoperative inflammation was evaluated at one and six weeks after surgery based on cell/flare scores. Mean scores at both visits were low in both study groups, but there was a significant benefit for adjunctive NSAID use.

The analyses of PCME incidence showed a statistically significant benefit of adding topical nepafenac to the corticosteroid in the overall study population.

Analyses after stratification of patients based on the absence or presence of purported PCME risk factors showed the rate of PCME was approximately four-fold higher in the subgroup with risk factors versus the subgroup without and that use of topical nepafenac had a significant benefit for reducing risk only in the subgroup with risk factors.

The data were also analyzed to determine the association between different clinical variables and risk of PCME. The results showed that a history of PCME in the fellow eye was the most powerful predictor, increasing the risk of PCME 20-fold. Diabetic retinopathy and vein occlusion were each associated with an approximately 13-fold increase in risk of PCME.

Having a macular hole increased the risk almost eight-fold and epiretinal membrane was associated with an approximately six-fold increase in risk. Use of a prostaglandin analogue or macular degeneration did not affect the risk of PCME.

"The lack of an association with prostaglandin analogue use was interesting but also consistent with the findings of a retrospective study that included 40,000 patients," Dr. McCafferty commented.

Patients enrolled in the study were also asked to complete the Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire. Analyses of the collected data showed a statistically significant benefit of the topical NSAID for reducing browache and tearing. There were no differences between study groups in analyses of any of the other items included in the questionnaire.

The results of an ESCRS-sponsored European multicenter trial of the prevention of cystoid macular edema after cataract surgery in nondiabetics in which adjunctive NSAID treatment had benefit for reducing clinically significant CME in nondiabetic patients [Wielders LHP, et al. ESCRS PREMED Study Group. *J Cataract Refract Surg*. 2018;44:429-439.]. Offering a possible explanation for the difference, Dr. McCafferty suggested it may be related to the use of different corticosteroids.

"The ESCRS study used dexamethasone 0.1%, and it has lower ocular tissue penetration than prednisolone acetate 1% that was used in the ASES and is more commonly used in the United States," he said. ■

> 'A survey conducted prior to designing the study showed that the primary reason most cataract surgeons were prescribing a topical NSAID was to reduce the risk of PCME, which is off-label use.'
>
> — *Sean J. McCafferty, MD*

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Dr. McCafferty has no relevant financial interests to disclose.

Special Report) LEADING-EDGE RESEARCH IN **ANTIBIOTIC AND ANTI-INFLAMMATORY DRUGS**

Intraocular corticosteroid a step forward for postop inflammation

Sustained-release option overcomes limitations of topically administered drops

By Cheryl Guttman Krader; *Reviewed by Eric D. Donnenfeld, MD*

APPROVED BY THE FDA last year, dexamethasone intraocular suspension 9% (Dexycu, EyePoint Pharmaceuticals) was officially launched in March.

As an investigator in premarketing clinical trials, Eric D. Donnenfeld, MD, began using the novel sustained-release corticosteroid three years ago.

Based on his experience and the advantages of the intraocular product, Dr. Donnenfeld said he is now using it routinely in all cataract surgery cases involving Medicare patients.

"Drug delivery for medications used in cataract surgery is changing dramatically, and dexamethasone intraocular suspension is an exciting advance that overcomes the limitations of topically administered drops," said Dr. Donnenfeld, clinical professor of ophthalmology, New York University Langone Medical Center, New York, NY, and founding partner, Ophthalmic Consultants of Long Island and Connecticut, Garden City, NY.

"It puts the surgeon in charge and takes the responsibility of the corticosteroid out of the hands of patients who may be unreliable or unable to administer their medication," he said. "Furthermore, it avoids the potential ocular surface toxicity of topical medications and their cost."

PASS-THROUGH STATUS

The dexamethasone intraocular suspension has been granted pass-through status and reimbursement by the Centers for Medicare and Medicaid Services, Dr. Donnenfeld noted.

'The intraocular product immediately delivers and maintains a therapeutic concentration for the corticosteroid at the target site.'

— Eric D. Donnenfeld, MD

As a result, dexamethasone intraocular suspension is provided at no cost to the surgery center, the surgeon, or Medicare patients with coinsurance, who represent about 90% of the Medicare population.

In the few months since the intraocular corticosteroid became commercially available, Dr. Donnenfeld said that he has used it with excellent safety and efficacy in about 100 eyes that underwent cataract surgery, including some complex cases.

"The intraocular product immediately delivers and maintains a therapeutic concentration of the corticosteroid at the target site," he explained.

That can be a key driver for physicians to consider to ensure positive results for patients.

"For that reason, I particularly like it in situations where there is likely to be an increased inflammatory response, such as in a case involving a sutured IOL or planned pars plana vitrectomy," he added.

USE IN GLAUCOMA SURGERY

For the same reasons, Dr. Donnenfeld said his partners are using it in glaucoma surgery.

"I am considering its use for keratoplasty cases," he added.

Dr. Donnenfeld said that he has seen a single patient who required rescue topical corticosteroid treatment to control inflammation, despite the routine use of a topical nonsteroidal anti-inflammatory drug (NSAID) in all cases.

Although there is a risk for IOP elevation with any corticosteroid, and IOP monitoring is necessary when using the dexamethasone intraocular suspension, the incidence of increased IOP in clinical trials was low, and Dr. Donnenfeld said that he has not encountered any patients who developed a postoperative IOP spike.

The intraocular corticosteroid is administered as an 0.005 mL injection behind the iris at the end of the case and following delivery of any intracameral antibiotic.

Dr. Donnenfeld offered the following tips to optimize retention of the material behind the iris:

- **Hydrate the surgical incision so that it is sealed—incision leak will draw the product into the anterior chamber.**
- **Place the tip of the delivery cannula behind the iris at 120° and move it inferiorly while rubbing tangentially along the back of the iris.**

According to Dr. Donnenfeld, migration of the medication into the anterior chamber does not seem to compromise efficacy nor interfere with vision.

Patients should be informed that they may notice the material and that it is not a cause for concern. ■

TAKE-HOME

- ***Dexamethasone intraocular suspension 9% (Dexycu, EyePoint Pharmaceuticals) was launched in March 2019. Its advantages make it a natural choice to routinely replace topical corticosteroid drops in all Medicare cataract surgery patients.***

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Dr. Donnenfeld is a consultant to EyePoint Pharmaceuticals and other companies marketing and developing products for treating inflammation after ophthalmic surgery.

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XELPROS™ (latanoprost ophthalmic emulsion) 0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XELPROS is contraindicated in patients with a known hypersensitivity to latanoprost, or any other ingredients in this product.

WARNINGS AND PRECAUTIONS

Pigmentation: XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Eyelash Changes: XELPROS may gradually change eyelashes and vellus hair in the treated eye, including increased length, thickness, pigmentation, and number of lashes. The changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema: XELPROS should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Herpetic Keratitis: XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses: Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS

The most common ocular adverse reactions in clinical trials (incidence ≥5%) for XELPROS were eye pain/stinging, ocular hyperemia, conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening.

DRUG INTERACTIONS

Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

Please see brief summary of Full Prescribing Information on the adjacent page.

BAK=benzalkonium chloride.

References: 1. XELPROS [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; 2018. **2.** Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.

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Brief Summary of Prescribing Information for XELPROS™ (latanoprost ophthalmic emulsion) 0.005%, for topical ophthalmic use

XELPROS™ (latanoprost ophthalmic emulsion) 0.005%
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INDICATIONS AND USAGE
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Use with Contact Lenses
Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Across multiple clinical trials conducted with XELPROS, the most frequently reported ocular adverse reactions were eye pain/stinging upon instillation and ocular hyperemia, reported in 55% and 41% of patients treated with XELPROS, respectively. Other adverse reactions reported (incidence ≥5%) were conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening. Less than 1% of patients discontinued therapy because of intolerance to the eye pain/stinging or to the ocular hyperemia.

DRUG INTERACTIONS
Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XELPROS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether latanoprost or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XELPROS is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XELPROS.

Potential for Eyelash Changes
Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XELPROS. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated emulsions.

When to Seek Physician Advice
Advise patients that if they develop an intercurrent ocular condition (eg, trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of the multiple-dose container.

Use with Contact Lenses
Advise patients that contact lenses should be removed prior to administration of the emulsion. Lenses may be reinserted 15 minutes following administration of XELPROS.

Use with Other Ophthalmic Drugs
Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

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SUN OPHTHALMICS

Knowledge is key for successful DALK procedure

Understanding corneal anatomy can minimize risk of Descemet's membrane rupture

By Cheryl Guttman Krader; *Reviewed by Sadeer B. Hannush, MD*

Knowledge of corneal ultrastructural anatomy that recognizes the presence of the pre-Descemet's layer (PDL) brings a new understanding to deep anterior lamellar keratoplasty (DALK) and its successful completion, said Sadeer B. Hannush, MD

Dr. Hannush, attending surgeon, cornea service, Wills Eye Hospital, and professor of ophthalmology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, explained that the PDL, which was first described by Professor Harminder Dua and colleagues in 2013,[1] lies immediately anterior to Descemet's membrane (DM), beneath the posterior stroma. Although it is only 5 to 15 µm thick, the PDL has a high bursting pressure of >500 mm Hg.

Dr. Hannush

Whether or not the PDL is left behind with the DM and endothelium after air injection to create the Big Bubble (BB) in DALK determines the risk of rupture into the anterior chamber.

"A BB type 1 (BB1) cleaves off or separates the posterior stroma from the PDL, leaving the PDL behind with DM and endothelium. In this scenario, there is little risk of perforation into the anterior chamber because the PDL has such a high bursting pressure," he said.

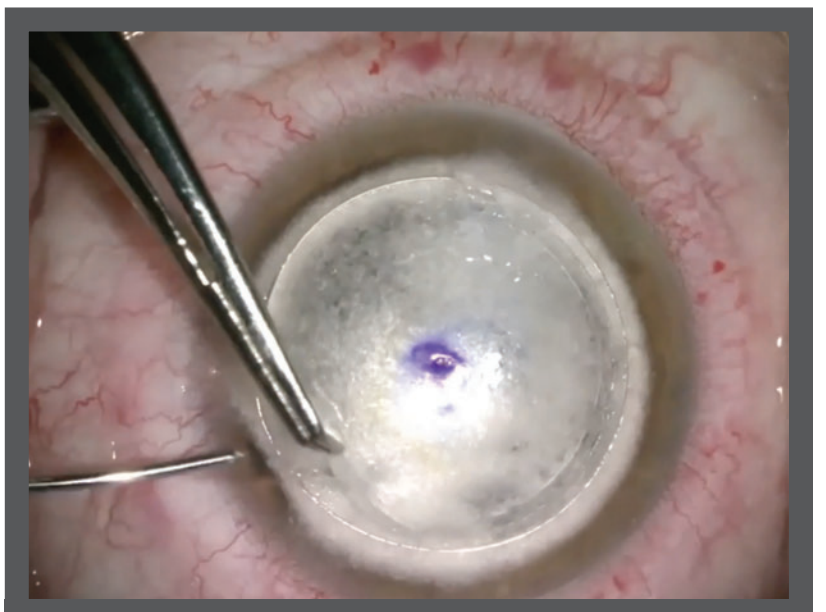
Dr. Hannush also noted that a Big Bubble type 2 (BB2) forms between PDL and DM, leaving behind DM and endothelium.

"In this situation, the risk of rupture into the anterior chamber is greater because the bursting pressure of DM is only around 30 mm Hg, and this risk remains increased during the remainder of the procedure due to the fragility of DM," he explained.

Dr. Hannush said that by allowing surgeons to identify the location of the cannula before injecting air to create the BB, intraoperative OCT is helpful for achieving a BB1. Surgeons who do not have access to this imaging tool may be able to judge whether a BB1 or BB2 was created based on how it is formed.

"In most instances, a BB1 develops from the center to the periphery whereas a BB2 develops from the periphery to the center," he said.

If there is a BB2, surgeons do not need to abort the DALK procedure and convert to penetrating keratoplasty. In this instance, Dr. Hannush noted that surgeons need to recognize that they are dealing with a more tenuous situation that requires patience and attention to detail in order to bring DALK to a successful completion.



Understanding corneal ultrastructural anatomy can bring a new understanding to deep anterior lamellar keratoplasty. In this image, air creates a Big Bubble. *(Image courtesy of Sadeer B. Hannush, MD)*

Dr. Hannush offered several pearls for proceeding in the setting of a BB2. To minimize the risk of DM rupture, he cautioned against touching DM with any instrument or squirting it with BSS.

Dr. Hannush also recommended injecting a cohesive viscoelastic between PDL and DM to create space and avoid inadvertent contact between the scissors and DM while removing the posterior stroma.

"Ideally, the viscoelastic device cannula may be replaced with the same cannula used to create the BB (eg., Sarnicola, Fogla, Tan, etc.)," he said, noting these cannulas are preferred because they have a smooth contour and a posterior opening that will push DM away from the cannula.

Dr. Hannush also advised use of rounded scissors to remove the posterior stroma/PDL after creation of BB2 and cautioned against "leaning" on DM with the posterior blade of the scissors. The Tan DALK scissors, which features a platform on the posterior blade, is designed specifically for this maneuver in cases of both BB1 and BB2.

"Before proceeding, however, ensure that the big bubble (1 or 2) extends to or beyond the trephination mark and that there are no adhesions between PDL and DM," Dr. Hannush concluded. "They can lead to rupture during removal of the posterior stroma (BB1) or the posterior stroma/PDL (BB2)." ■

TAKE-HOME

- ***Knowledge of the presence and characteristics of the pre-Descemet's layer provides a foundation for the understanding of tissue separation during deep anterior lamellar keratoplasty that will minimize the risk of rupture with Big Bubble creation and during the remainder of the procedure.***

REFERENCE

1. Dua HS, et al. *Ophthalmology.* 2013;120:1778-1785.

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This article was adapted from Dr. Hannush's presentation during Cornea Day at the 2019 meeting of the American Society of Cataract and Refractive Surgery. Dr. Hannush has no relevant financial interests to disclose.

NEW

The first and only FDA-approved, single-dose, sustained-release, intracameral steroid for the treatment of postoperative inflammation[1-3]

With a single injection at the end of cataract surgery, anti-inflammatory efficacy begins as early as day 1 and continues through day 30[1]*

- The percentage of patients who received DEXYCU (517 mcg) who had anterior chamber cell clearing on day 8 was 60% (n=94/156) vs 20% (n=16/80) in the placebo group[1]
- The cumulative percentage of subjects receiving rescue medication of ocular steroid or nonsteroidal anti-inflammatory drug (NSAID) at day 30 was significantly lower in the DEXYCU (517 mcg) treatment group (20%; n=31/156) compared to placebo (54%; n=43/80)[1]

NOW AVAILABLE

DEXYCU™
(dexamethasone intraocular suspension) 9%

*DEXYCU was studied in a randomized, double-masked, placebo-controlled trial. Patients received either DEXYCU or a vehicle administered by a physician at the end of the surgical procedure. The primary endpoint was the proportion of patients with anterior chamber cell clearing (cell score=0) on postoperative day 8.

INDICATION AND USAGE

DEXYCU™ (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

- Prolonged use of corticosteroids, including DEXYCU, may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision
- Steroids should be used with caution in the presence of glaucoma

Delayed Healing

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids

Exacerbation of Infection

- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures
- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection

Cataract Progression

- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts

ADVERSE REACTIONS

- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. DEXYCU™ (dexamethasone intraocular suspension) 9% full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. December 2018. **2.** Donnenfeld E, Holland E. Dexamethasone intracameral drug-delivery suspension for inflammation associated with cataract surgery: a randomized, placebo-controlled, phase III trial. *Ophthalmology.* 2018;125(6):799-806. **3.** Data on file. EyePoint Pharmaceuticals, Inc.

EyePoint™ PHARMACEUTICALS

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480 Pleasant Street, Suite B300, Watertown, MA 02472

01/2019
US-DEX-1900045

DEXYCU (dexamethasone intraocular suspension) 9%,
for intraocular administration
Initial U.S. Approval: 1958

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE
DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure
Prolonged use of corticosteroids including DEXYCU may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma.

5.2 Delayed Healing
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids.

5.3 Exacerbation of Infection
The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection.

5.4 Cataract Progression
The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS
The following adverse reactions are described elsewhere in the labeling:
- Increase in Intraocular Pressure *[see Warning and Precautions (5.1)]*
- Delayed Healing *[see Warnings and Precautions (5.2)]*
- Infection Exacerbation *[see Warnings and Precautions (5.3)]*
- Cataract Progression *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively *[see Data in the full prescribing information].*

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation
Risk Summary
Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use
Safety and effectiveness of DEXYCU in pediatric patients have not been established.

8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between older and younger patients.

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472

DEX0019

Three-step surgery allays aging, fatigue in lower lid procedure

Dual-plane blepharoplasty can improve tear trough, skin, lower lid position

By Lynda Charters; *Reviewed by Martin H. Devoto, MD*

In contrast to upper lid blepharoplasty—which is considered a surgically simple procedure when given the appropriate attention to detail—that of the lower lid is one of the most complex facial cosmetic procedures performed, said Martin H. Devoto, MD.

With aging and fatigue reflected in the lower eyelid area, the key elements to achieving a youthful contour in the lower lid is providing a short vertical lower lid.

"After each decade, the length of the lower lid increases," explained Dr. Devoto, director, Oculoplastics and Orbital Surgery Division, Consultores Oftalmologicos, Buenos Aires, Argentina. "A short lower lid is a sign of youth."

Dr. Devoto

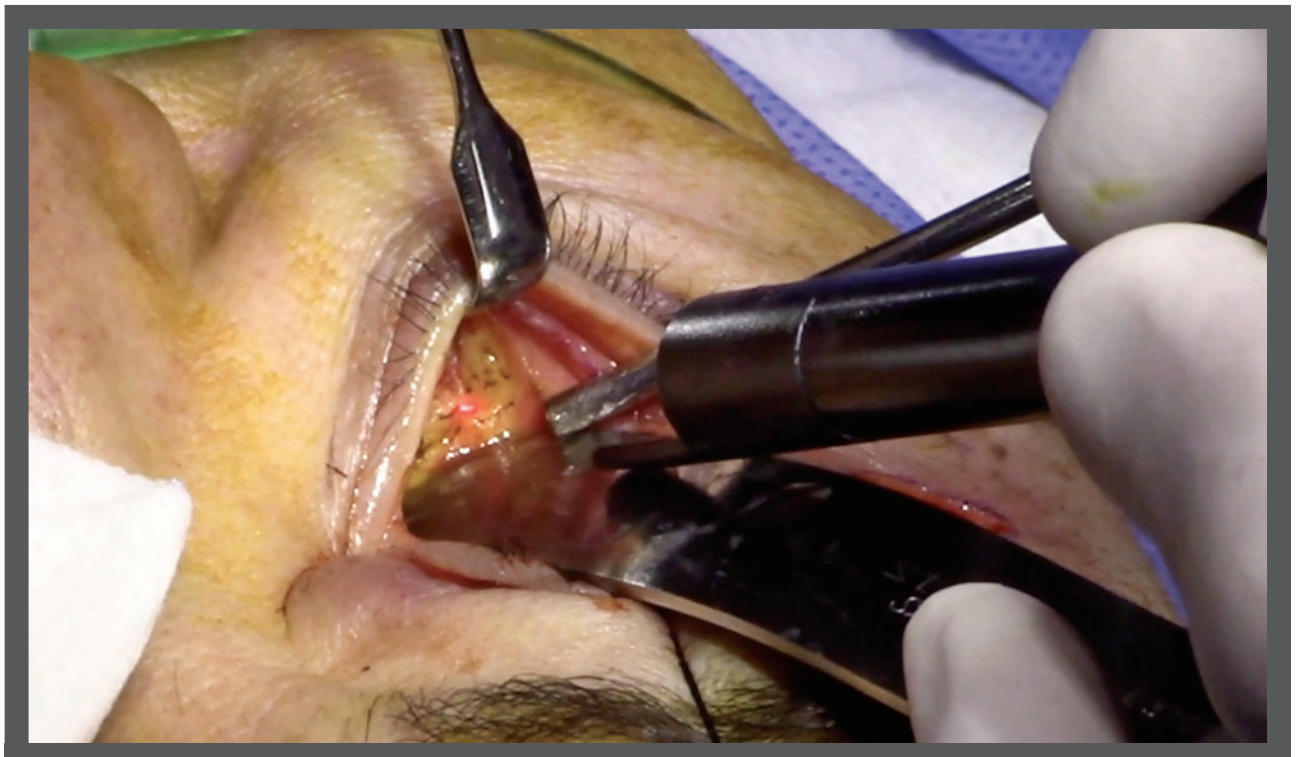
Another element is the preservation and enhancement of the shape of the lower lid. In younger patients, the lateral canthal angle of the lower lid is higher than the medial compared with older patients.

The final element that should be enhanced is the quality of the skin, he noted.

THREE PARTS

To reach these goals, Dr. Devoto and colleagues perform a three-part combination procedure—the dual-plane blepharoplasty.

- **The first part is improving the tear trough with fat transposition.**
- **The second part is tightening the orbicularis muscle to improve laxity by placing a stitch that is passed from the superior incision above when performing an upper lid blepharoplasty or by making a separate stab incision, grasping the orbicularis muscle, and tightening it to the upper lid.**
- **The third component is improving wrinkles using a skin-pinching technique, which preserves the orbicular muscle function and innervation by avoiding cutting the muscle, Dr. Devoto explained.**



VIDEO **Watch the procedure. Go to OphthalmologyTimes.com/LowerLid** *(Video courtesy of Martin H. Devoto, MD)*

Dr. Devoto makes a cut with a monopolar needle or CO_2 laser after the lower lid is retracted. He performs the dissection in front of the septum to avoid bulging of the fat.

Dr. Devoto notes the importance of placing a corneal shield, but before that, he puts a stitch in the conjunctiva and places retractors for better exposure. He dissects inferior to the arcus marginalis, for about 10 mm and completely release the orbital retaining ligament.

He advises paying attention to the exit point of the infraorbital nerve, and the dissection can be aided using a cotton swab. When the pocket is formed, the medial and central fat pads are released in pedicules and freed using Wescott scissors. A 5-0 nylon suture is inserted about 10 mms below the premarked arcus marginalis. The suture goes under the dissected flap and it is used to engage the medial and central fat pads to create a "curtain" of fat.

The fat creates a layer that will hold and help elevate the tear trough, Dr. Devoto explained.

The exit point is located slightly nasally. A pearl at this point is to avoid overtightening the 5-0 nylon stitch, which is removed 1 week postoperatively.

The lateral fat pad can be transposed in some patients, but in these cases, a dissection is necessary in the lateral area. However, this increases the degree of chemosis. Because of this, he usually opts to excise this fat.

TAKE-HOME

- ***Lower lid blepharoplasty is one of the most complex facial cosmetic procedures performed, in contrast to upper lid blepharoplasty. Martin H. Devoto, MD, shares his surgical pearls.***

A final step in the procedure is pinching of the skin, which is removed with a Wescott scissors to the point of the inferior punctum. To raise the orbicularis muscle, he engages the periosteum by passing a suture, which goes beneath the orbicular muscle and exits through pinched tissue to produce a mild elevation of the canthal elevation. The knot is buried under the orbicularis muscle.

"The key points in this procedure are marking the extent of the tear trough and dissecting and releasing of the entire tear trough, careful and complete release of the fat pedicles with no or partial exci-

Continues on page 23 : ***Dual-plane***

CORNEAL

(Continued from page 1)

the people in the world affected by corneal blindness never have any opportunity for treatment to restore vision," Dr. Shiuey said. "There exists a big mismatch between the availability of corneal tissue for transplantation and the number of patients in need of a corneal transplant, and yet very few artificial corneas are being implanted."

There is also a lack of trained corneal transplant surgeons worldwide and few sterile operating rooms that are properly equipped for the procedure, he added.

"Although the Boston keratoprosthesis offers an alternative to corneal transplantation, donor tissue is still needed for implantation," Dr. Shiuey said.

"It is associated with severe complications that limit it from being widely utilized," he said. "If we could change this dynamic, we could potentially treat all of the patients in the world who are affected by corneal blindness."

TAKE-HOME

- ***Drawbacks and limitations of penetrating keratoplasty and penetrating keratoprosthesis prevent their widespread use to treat the tens of millions of people with corneal blindness. A non-penetrating artificial cornea was designed to overcome the impediments.***

DIVING DEEPER

The non-penetrating keratoprosthesis has an overall diameter of 7 mm and has a 4 mm central optic.

"The optic provides a full visual field and its prescription is also potentially customizable," Dr. Shiuey said.

The device is implanted through a 3.5 µm trephination incision into an 8-mm corneal pocket that is created at about 100 µm above the endothelium using a femtosecond laser.

"The keratoprosthesis cannot be implanted without a very precise way to make the corneal pocket, and so the pocket cannot be created manually," he said.

"The recommended method of pocket creation is with a femtosecond laser, which is widely available around the world," he said. "For those places that do not have access to femtosecond lasers, there are commercially available non-laser devices that can be used for precise pocket creation."

The procedure does not need to be performed in an operating room, nor does it require concomitant glaucoma surgery that is often performed in cases of penetrating keratoprosthesis implantation, Dr. Shiuey emphasized.

"The procedure can be performed in a clean office environment, and it has a short learning curve," he said.

CLINICAL EXPERIENCE

A review of outcomes in 26 patients who were previously blind showed that 92% were able to achieve 20/200 or better vision. Improvement in vision occurred quickly after surgery, stabilized within one to two months, and remained unchanged during a mean follow-up at 50 months.

The safety review showed an 11% extrusion rate. Other complications included one case of corneal melting in a patient with a diagnosis of chemical burn and one infection in a patient who was not compliant with the postoperative regimen.

"There were no cases of endophthalmitis, retroprosthetic membrane, or increased IOP, which are the serious complications that traditionally happen with penetrating keratoprostheses," Dr. Shiuey said.

The outcomes were replicated in another series reported by Jorge Alio, MD, PhD, that included 15 patients [Alio JL, et al. *Br J Ophthalmol.* 2015;99:1483-1487].

"There were also no cases of endophthalmitis, retroprosthetic membrane, or increased IOP in this smaller cohort," noted Dr. Shiuey, adding that Dr. Alio also commented that the "KeraKlear keratoprosthesis is a noninvasive viable alternative to corneal transplantation with potential advantages like decreased risk of endophthalmitis, expulsive hemorrhage, and worsening glaucoma."

The development of the non-penetrating keratoprosthesis is supported in part with funding from the National Institutes of Health. The FDA trial is investigating its use in patients with corneal opacity that are at high risk of complications with penetrating keratoplasty.

The study is being conducted at four U.S. centers, including Harvard Medical School; the Gavin Herbert Eye Institute, University of California-Irvine; Duke Eye Center; and the Cincinnati Eye Institute. Dr. Shiuey encouraged his colleagues to refer potentially eligible patients for screening. ■

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This article was adapted from Dr. Shiuey's presentation during the Innovators General Session at the 2019 meeting of the American Society of Cataract and Refractive Surgery. As the inventor, Dr. Shiuey has a financial interest in the KeraKlear artificial cornea.

DUAL-PLANE

(Continued from page 22)

sion to avoid tension, and identification of the inferior oblique muscle to make sure the medial and central fat pockets are not attached to the muscle," he said.

Dr. Devoto and colleagues conducted a study that included 200 consecutive patients who underwent this procedure in two centers in Argentina and Italy performed by two surgeons (Dr. Devoto and Dr. Francesco Bernardini, MD).

An oculoplastics specialist evaluated the changes in the tear trough and a dermatologist assessed the changes in wrinkling on photographs from preoperatively to postoperatively.

The changes in the lower lid position were analyzed using validated software and compared with controls who ranged in age from 25 to 35 years.

"Using the software, we were able to show that the distance in the eyelid margin decreased significantly [$p < 0.05$] after surgery in both the vertical mid-pupillary distance and the medial and lateral radius," he said.

Ninety percent of patients had skin improvement; 96% had tear trough improvement; and 75% had good to excellent outcomes.

Complications can include remaining bags under the eyes, irregularities in the correction, and insufficient transposition of the tear trough.

"The dual-plane blepharoplasty can improve the tear trough, the skin, and the lower lid position," Dr. Devoto concluded. ■

> 'We were able to show that the distance in the eyelid margin decreased significantly [$p < 0.05$] after surgery in both the vertical mid-pupillary distance and the medial and lateral radius.'
>
> *– Martin H. Devoto, MD*

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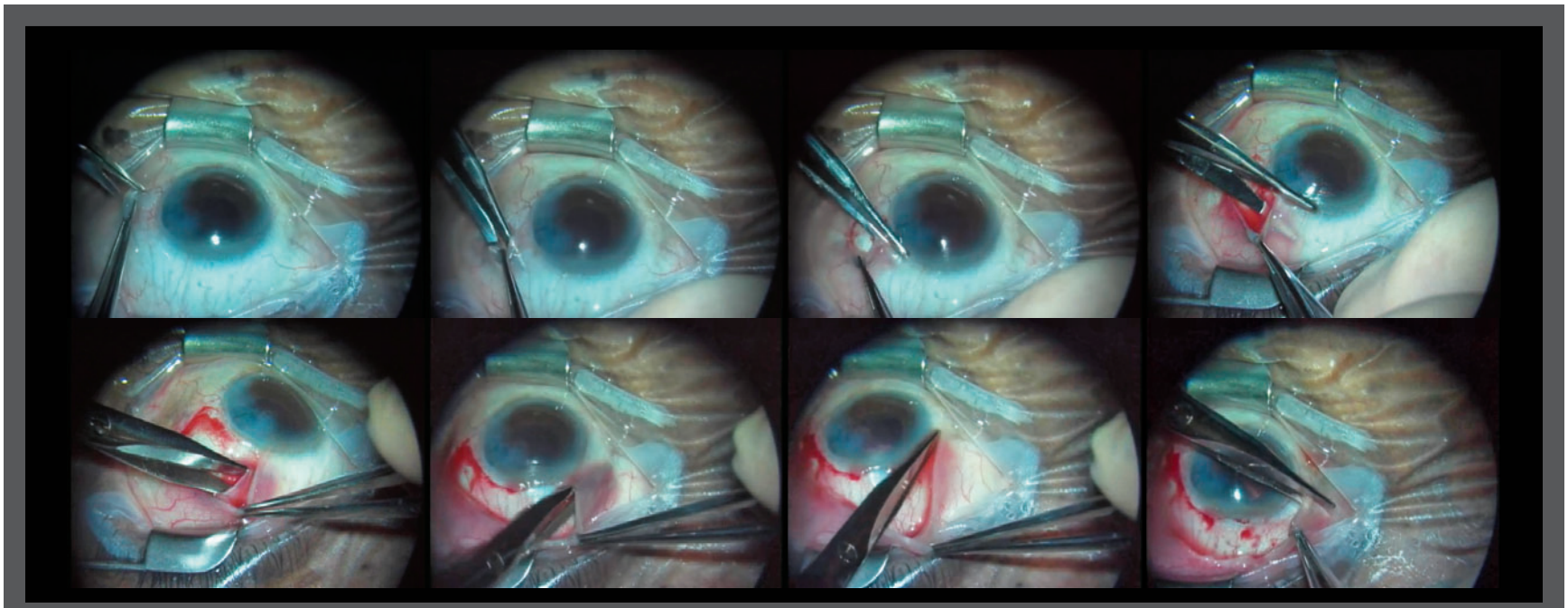
This article was adapted from Dr. Devoto's presentation during Oculoplastics Subspecialty Day at the 2018 meeting of the American Academy of Ophthalmology. Dr. Devoto has no financial interest in any aspect of this report.

Physicians share surgical pearls for successful trabeculectomy

Several techniques can result in better surgical outcomes for patients

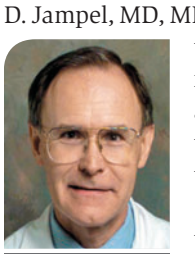
By Cheryl Guttman Krader; *Reviewed by Paul Palmberg, MD, PhD, and Henry D. Jampel, MD, MHS*



To avoid bleeding in the area of filtration, cut the conjunctival Tenon's capsuile flap. *(Photos courtesy of Paul Palmberg, MD, PhD)*

VARIATIONS IN trabeculectomy technique aim to optimize long-term IOP control and minimize the risk of early and late complications.

Paul Palmberg, MD, PhD, and Henry D. Jampel, MD, MHS, shared elements they have incorporated in their surgical approach that contribute to successful trabeculectomy.



Dr. Palmberg

Dr. Jampel

Dr. Palmberg said that his current technique has been developed during a career of more than 40 years.

"In a large group of patients, it has achieved long-lasting IOP control in the low-normal range with no net visual field progression over a decade of follow-up, and it has been associated with a low rate of hypotony," said Dr. Palmberg, professor of ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL.

The first consideration is how to avoid bleeding and the need for excessive cautery, both of which promote scarring, he reported.

AVOIDING BLEEDING

To avoid bleeding in the area of filtration, he cuts the conjunctival-Tenon's capsule flap only far away from the filtering site, beginning with a lateral relaxing incision down to sclera, demonstrated in the photo above.

Dr. Palmberg said he then everts the conjunctiva and passes the Westkott scissors behind the insertion of Tenon's capsule, which is 1-2 mm behind the insertion of the conjunctiva, in order to enter the potential space under Tenon's.

The scissors are then advanced under Tenon's, lifting it above the scleral surface vessels, pulled down toward the limbus, and then one blade is inserted and the conjunctiva and Tenon's capsule are cut together at their insertions.

"The only bleeding is at the insertions, where spot cautery can be applied," Dr. Palmberg said. "This avoids the problem that I see with smaller conjunctival flaps, in which the scissors pass blindly under the flap and cut into the vessels in Tenon's, and mitomycin-C (MMC) sponges come out soaked in blood."

He then uses the scissors to penetrate through the intermuscular septum to each side of the superior rectus.

MMC 0.4 mg/ml is then applied using large (4 x 4 mm) thin pieces of cellulose sponge cut from a spear sponge. The sponges are placed through the opening in the intramuscular septum to each side and along the limbus.

The sponges are removed after 3 to 5 minutes and inspected to see that they are intact. Then, the eye is rinsed with 5-10 ml of saline.

"I have found that the wide application of MMC, introduced by Sir Peng Khaw, greatly reduced bleb problems by producing more diffuse blebs," he said.

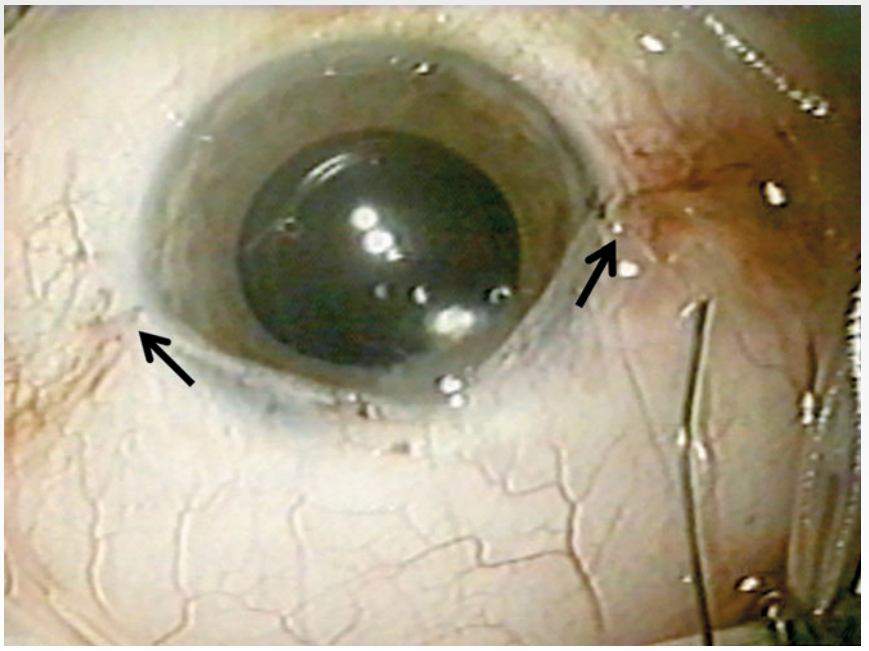
Dr. Palmberg added that prior to MMC application, he creates a "safety-valve" tunneled trabeculectomy.

In this technique, a 3-mm groove is made at two-thirds depth in the 12

TAKE-HOME

- ***Glaucoma surgeons highlight elements of their personal trabeculectomy technique, which can optimize long-term IOP control and minimize the risk of early and late complications.***

How to Achieve a Watertight Conjunctival Closure



Closure to each side with knots buried:

1. **Mattress at limbus**
2. **Continue as running to apex of relaxing incision**
3. **Back under to tie underneath.**

Snug, not bunched

(Photo courtesy of Paul Palmberg, MD, PhD)

o'clock position, 1 mm behind clear cornea. Then a crescent knife is used to tunnel 2 mm forward, 1 mm into clear cornea. A bent paracentesis blade is then used to enter the anterior chamber, and a 0.75 mm Kelly Decemet's punch is used to punch out two side-by-side pieces of the posterior lip of the internal ostium. Balanced salt solution is then injected into the anterior chamber to inflate it and to initiate aqueous flow.

The flow is observed to equilibrium, using a cellulose spear sponge to gently touch the groove to absorb fluid, and then the points of light in the groove are watched as they disappear as fluid fills the groove.

The IOP at equilibrium flow is estimated by pushing on the cornea with a 30-gauge cannula, with a goal of having this wound set an IOP of about 4-6 mm Hg, Dr. Palmberg said.

ADDITIONAL PUNCHES

Additional punches or cutting down on the sides of the tunnel are then performed until that goal is reached. Two 10-0 nylon sutures are then placed and their tension adjusted to yield an equilibrium IOP estimated at 8-12 mm Hg.

"That this is an effective means of adjusting the scleral resistance is confirmed by the observed mean IOP of 10 mm Hg on day 1 postop," Dr. Palmberg said.

The conjunctival flap is then closed with a buried 10-0 nylon mattress suture at 12 o'clock. Buried mattress sutures of 8-0 polyglactin 910 (Vicryl) are placed at 3 and 9 o'clock, with the conjunctiva-Tenon's capsule pulled tight along the limbus to be impaled upon the emerging needle.

The suture is then continued as a running suture to the end, and an apical bite is passed back under the flap on each side to be tied underneath the flap, so that the single knot to each side is buried, with a snug and water-tight closure, without bunching the tissue.

SCLERAL BITES

Dr. Palmberg emphasized that the scleral bites of the closure need to pass vertically into the tissue, then pass along in sclera, and also exit as vertically as possible, producing "square wave bites," rather than skimming bites, in order for the fragile conjunctiva to be supported and not torn.

Considering fashion stitches, Dr. Palmberg said he wondered how seamstresses could sew a fragile material like silk without having the thread claw holes.

"Looking at the inside of a seam in my wife's silk dress I saw seam binding tape and noted that the seamstress aligns passes through the tape with passes through the silk on each side so that the closure compresses, but does not tear the material," he explained. "If you do not similarly support the conjunctiva with matched scleral bites, your sutures will gradually claw through the scleral bite at the skimming entry and exit and loosen the conjunctival closure, typically leading to a limbal leak at about three days."

Dr. Palmberg said that his technique is fairly efficient, involves no device cost, and obviates the need for an iridectomy because there is no flow until the anterior chamber is formed.

In addition, the technique also is associated with less induced astigmatism because the flap sutures do not need to be very tight.

"But most important are the outcomes showing it has achieved an average IOP of 11 mm Hg over a decade of follow-up with no net field loss in the group, and a success rate, defined by an IOP < 15 mm Hg, of 90% at two years, 73% at five years, and 60% at 10 years," he said.

MORE PEARLS

Highlighting a few steps in his trabeculectomy technique, Dr. Jampel, Odds Fellows professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, said he initiates the conjunctival peritomy 1.5 to 2 mm posterior to the limbus, a technique he learned from Eugenio Maul Jr., MD, and places a 50/50 mixture of lidocaine and bupivicaine through the snip incision for local subconjunctival anesthesia.

When applying MMC, Dr. Jampel uses an 0.2 mg/mL concentration and places it through the snip incision. He opens up the incision so that it is parallel to and about 2 mm posterior to the limbus.

Dr. Jampel then performs the conjunctival dissection posteriorly and to the sides.

After the trabeculectomy flap has been made, Dr. Jampel preplaces two releasable sutures of 10-0 nylon using a technique shown to him by Jayant Iyer, MD, a fellow who came from Singapore.

SINGAPORE SLING

"I have named this technique the Singapore sling releasable suture. It is made by placing a backhanded suture that starts in the sclera, comes out through the cornea, and then goes back in through the flap," explained Dr. Jampel.

After completing the scleral flap dissection, creating a sclerotomy with a Kelly Descemet's punch, and iridectomy, he then sutures the flap with the releasable sutures and places a third releasable suture anchored in the cornea.

He said he then closes the conjunctiva with two 10-0 nylon wing sutures whose knots are buried.

"I feel that by pulling the posterior lip up against a residual 'bolster' of conjunctiva at the limbus, I can achieve a watertight closure without the need for a central suture," Dr. Jampel concluded. ■

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This article was adapted from Dr. Jampel's presentation at the 2019 American Glaucoma Society annual meeting. Dr. Jampel has no relevant financial interests to disclose.

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This article was adapted from Dr. Palmberg's presentation at the 2019 American Glaucoma Society annual meeting. Dr. Palmberg has no relevant financial interests to disclose.

Neuropathic corneal pain: The new 'umbrella'

Focus of dry eye may shift to ocular surface issues that can cause discomfort in patients

By Lynda Charters; *Reviewed by Anat Galor, MD*

The term "dry eye" does not represent one disease but rather is an umbrella term that covers factors that may be unrelated to each other. When considering dry eye symptoms, there is a mix of pain and visual disturbances, which are not necessarily driven by the same underlying factors, said Anat Galor, MD, associate professor of ophthalmology, Bascom Palmer Eye Institute, University of Miami, Miami.

Dr. Galor

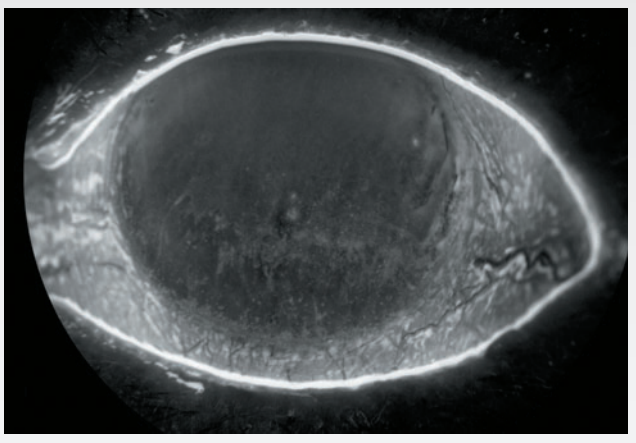
Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, she said. The word "pain" may prompt a barrage of descriptors to come to mind, such as burning, sharp, or dryness, all words that are used by patients to describe numerous sensations, all of which can induce a negative emotional response.

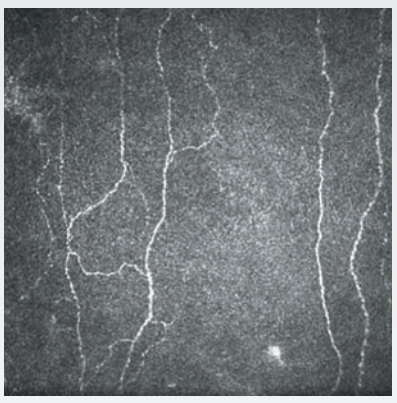
In the context of dry eye disease, the word pain, i.e., ocular surface pain, should scream "unhappy nerves," to clinicians. Many pathologies can make nerves "unhappy," including abnormal anatomy and medication toxicity. While patients may present with the complaint of ocular dryness, they may not have dry eye disease, according to Dr. Galor. Physicians have to look outside the tear film in some patients.

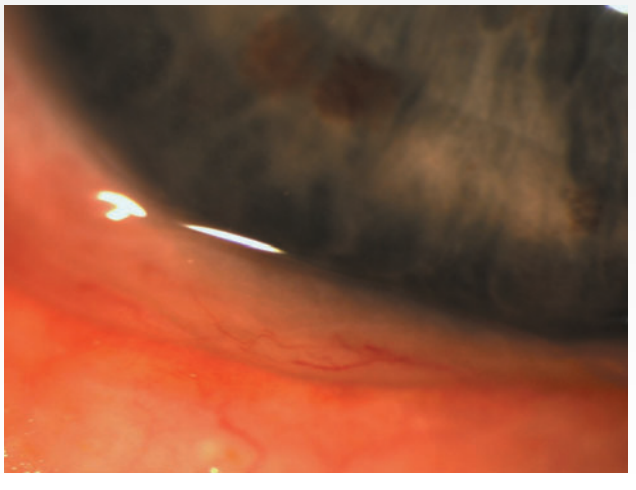
She described a patient who complained of extreme sensations of dryness but in actuality had redundant inferior conjunctival folds and a central expanded tear lake. It is a hallmark of conjunctrivochalasis, characterized by loose or redundant bulbar conjunctivae that drape over the lower eyelid margin. Examination after application of fluorescein showed that the nasal and temporal areas usually occupied by the tear lake were obliterated by conjunctiva.

Any conjunctival issue, such as a pterygium or an elevated bleb, can cause dry eye symptoms. Any eyelid issue can cause dry eye symptoms. She advised that physicians look for eyelid laxity and spastic entropion.

Drugs are another cause of dry eye symptoms, as can be seen in patients being treated for glaucoma. Other causes of dry eye symptoms are aqueous and evaporative tear deficiency. All are factors that cause nociceptive pain. A consideration often overlooked is nerves that can become dysfunctional and transmit signals inappropriately, i.e., neuropathic pain.







Left top: Corneal staining can correlate with visual function in dry eye. Above: A confocal microscopy image can serve as a diagnostic tool when treating patients. Bottom left: Conjunctrivochalasis is shown in a patient. *(Photos courtesy of Anat Galor, MD)*

Dr. Galor noted her steps for identifying the type of pain that patients are experiencing.

Step 1 is conducting a standardized workup by evaluating the symptoms, which includes an understanding of whether the patient is complaining of pain or vision complaints, chronicity, and pain quality.

"Clues that a patient may have a neuropathic component to the pain are complaints of burning, hyperalgesia, for example, from sensitivity to wind, and allodynia," Dr. Galor noted.

Step 2 involves the investigation of possible systemic issues that might be causing pain.

Step 3 is a fast, but complete ocular surface examination. A fluorescein strip can provide information about tear volume and break-up time, staining, eyelid issues, and anatomic abnormalities.

Step 4 considers the presence of persistent pain after instillation of a drop of anesthesia.

TAKE-HOME

- ***Corneal pain is multifactorial and clinicians should look beneath the surface to determine potential sources and solutions.***

Continues on page 27 : ***Dry eye***

Retinal detachment: No time like the present or sleep on it?

Anatomic changes after RD might help determine best time for surgery

By Lynda Charters; *Reviewed by Kirk H. Packo, MD*

TIMING IS EVERYTHING, even in relation to how quickly retinal detachments (RDs) should be repaired.

Dr. Packo

But what factors go into determining the optimal surgical time? A look at the anatomic changes that ensue after RD might help answer that question, according to Kirk Packo, MD, professor and chairman, Department of Ophthalmology, Rush University Medical Center, Chicago.

ANATOMIC CHANGES

A cascade of events takes place after a detachment, the first of which is development of cystoid macular edema followed by retinal degeneration. A study of owl monkeys showed that two variables were recognized over time: the time and height of the detachment. The photoreceptors begin to change within a day of the detachment. They fragment, become irregular, and rupture. The cells die within 14 days, Dr. Packo said.

Although the RPE have their normal blood supply under a detachment, they also are affected. The retinal pigment epithelium (RPE) microvilli retract and the surface becomes rounded.

"If the retina is put back in place, time is required for recovery," he said.

When the retina is reattached, the edema begins to resolve at one day in the owl monkey. However, the outer segments and RPE take more time.

Dr. Packo demonstrated that in cats the rhodopsin antibody is seen throughout the retina 28 days after a detachment. The bipolar cells begin to sprout and Mueller cells proliferate at three days, which becomes marked by the seventh day. By 28 days, a glial scar has formed throughout the inner retina, which explains the lack of visual recovery, Dr. Packo pointed out.

In the outer segments, change happens fast, i.e., within an hour, and they shorten considerably over time. By 28 days after reattachment, they have still not normalized.

WHAT TO LOOK FOR

There are preoperative factors that determine retinal recovery in humans.

DURATION: Ross et al. (*Ophthalmology.* 1998;105:2149-53) compared the durations of macula-off RDs in groups treated surgically one to two days, three to four days, and five to seven days after detachments. Interestingly, the vision in the three groups was a mean of 20/60 (p = 0.5) (mean follow-up, 10.5 months), suggesting that repairing a macula-off detachment within seven days does not affect the final vision.

Another study (*Ophthalmology.* 2002;109:146-56) looked at postponing surgery for more than one week (range, one day to six weeks) in 94 cases of macula-off detachments. The investigators found that the best results were achieved within 10 days of the detachment and younger patients fared better. The vision at 11 days to six weeks was 20/40 in 27% of cases compared with 20/40 in 71% at 10 days or sooner and 20/40 in 14% after six weeks after the detachment, Dr. Packo noted.

"The results indicate that there should really be no rush to the operating room," he said.

TAKE-HOME

- ***After detachment, development of cystoid macular edema and retinal degeneration occur, making time a key element in treatment.***

HEIGHT: A study (*Retina.* 2005;25:434-53) of 20 cases with a macula-off detachment reported the final vision was correlated negatively with height, distance from the fovea to the closest attached retina, and the extent of structural changes in the detached retina. The authors found a significant difference at nine months in vision between shallow and highly detached cases, 20/40 and 20/63, respectively.

TECHNIQUE: Among the three techniques for treating detachments, pneumatic retinopexy, buckling, and vitrectomy, a comparison of the first two showed identical results, 98% and 99% overall success, respectively (*Ophthalmology.* 1989;96:772-83). In cases of macula-off detachments pneumatic retinopexy achieved a vision of 20/50 in 80% compared with 56%.

MAKING A COMPARISON

When vitrectomy and buckling were compared (*Retina.* 2005;25:957-64), no differences in anatomic success or vision were found (83% versus 94% and 20/45 versus 20/40, respectively). Another study (*Jpn J Ophthalmol.* 2000;44:538-49) also reported that the two procedures were equivalent; however, in vitrectomy patients with macula-off detachments longer than one week vitrectomy achieved better results than buckling.

Buckling stills holds its own as evidenced by the PRO Study that included 2,168 cases of uncomplicated RDs; phakic patients achieved better vision with buckling versus vitrectomy or vit/buckle, and in pseudopha-

Continues on page 28 : ***Retina***

DRY EYE

(Continued from page 26)

Once information has been gathered, Dr. Galor said she evaluates it. She first treats the nociceptive sources of pain, such as inflammation and lid margin disease.

"If that does not relieve the pain, I move on," she said.

Corneal nerve modulation, especially with use of autologous tears, may help treat dysfunction nerves because nerve growth factor may help spark nerve regeneration after injury.

When central nerve abnormalities are involved, it must be determined if topical therapies are sufficient to alter peripheral and lateral central nociceptor function.

In cases in which central nerve abnormalities are involved, Dr. Galor noted using oral therapy consisting of pregabalin and gabapentin in isolation or in combination with serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine) to centrally modulate the system.

Dr. Galor said she has had success with adjuvant therapies. The emotional component of pain often goes unconsidered. Coping strategies may be acceptance-based, from relaxation therapies to hypnosis.

"Instead of focusing on dry eye, a new umbrella to consider is that of ocular surface pain, and numerous factors fall under that umbrella," she concluded. ■

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Dr. Galor has no financial interest in any aspect of this report. She is a consultant to Allergan and Novaliq.

Determining DR progression: Searching for the right choice

Modeling studies needed for clinicians to reliably predict changes

By Lynda Charters

THE WORLDWIDE INCIDENCE of diabetes has been increasing markedly, and by 2014 it affected 422 million people, up from 108 million in 1980. Amid that explosion in affected individuals, both the numbers of patients with diabetic retinopathy (DR) detected as a result of improved technology, and those who need treatment services also have increased.

Different countries handle management of these patients in different ways. For example, in the United States, annual screening is recommended for all patients with type 2 diabetes from the time of diagnosis. For those with type 1 diabetes, annual screening is also recommended, beginning five years after diagnosis.

In the United Kingdom, the diabetic eye screening program annually screens all patients over 12 years of age. Patients also are managed in hospital eye services. Patients with a low risk of DR remain within the diabetic screening program for annual surveillance. If their risk increases to sight-threatening DR, the hospital eye service provides frequent monitoring and treatment.

In both cases, there is a demand for treatment services. As a result, prognostic prediction models of DR are being used to optimize services. However, as one group of investigators pointed out, these models were intended initially to detect sight-threatening DR, and are used mostly in DR screening services.

REVIEW STUDY

In light of this, Sajjad Haider, MBBS, FRCS, FRCOPHTH, MSc, and colleagues conducted a review study "to summarize the characteristics and performance of existing models in predicting progression of retinopathy and their applicability for higher-risk DR patients under hospital care to predict need for treatment or loss of vision."

The investigators, who are from the Institute of Applied Health Research, University of Birmingham, Birmingham, UK, and York Teaching Hospital NHS Foundation Trust, York, UK, reported their findings in *Eye* 2019;33:702-13.

They searched MEDLINE, EMBASE, and COCHRANE CENTRAL, abstracts from conferences, and references lists for studies related to diabetes, DR, and prognostic models. They ultimately identified 22 articles that reported on 14 prognostic models that included four updates of the models that met their study criteria.

TAKE-HOME

- ***Primary modeling studies that are well-structured and easy-to-use are needed for clinicians to reliably predict progression of diabetic retinopathy, need for treatment, and visual loss.***

RESULTS

"Six models had both internal and external validation, five models performed only internal validation, and two were only validated in external datasets," the investigators reported. "One model lacked both internal and external validation. No studies assessing the impact of a model were identified. All studies were conducted during the last two decades."

The study sample sizes were large, ranging from 1,441 to 454,575 patients in the studies of primary development and from 200 to 206,050 in validation studies. The models included 78 different candidate predictors, with biochemical predictors being the most common.

Hemoglobin A1c [HbA1C] was the most common predictor, followed by the duration of diabetes, and three forms of age (current age, age at time of diabetes diagnosis, and age at time of DR diagnosis). Eleven models used local predictors/ocular signs, and one model used only ocular signs of prediction. The baseline DR was categorized as R0 in eyes, R1 in one eye, or R1 in both eyes.

The studies ranged from low to high risk of bias, with most having a high risk of bias and doubtful applicability. Most models focused on patients with lower risk, the authors noted.

ASSESSING RISK

The authors identified three models[1-3] with some applicability for patients at higher risk. These models had moderate to low risk of bias and a low risk for applicability and have already shown some impact in diabetic screening in lower-risk patients, the authors pointed out. The three models have shown that individual patient's risk assessment and prediction can be safely and effectively achieved through the use of routine data in patients with sight-threatening retinopathy.

Continues on page 29 : ***Progression***

RETINA

(Continued from page 27)

kic patients had higher single-surgery success with buckling compared with the other two.

Other factors are persistent fluid and macular displacement. The former can take up to two years to resorb but final vision is unaffected if the RD is shallow. Unintentional retinal displacement with resulting ghosting of vision was reported to be related to the RD extent and how much of the macula was unattached.

Non-surgical enhancement of macular recovery can prevent apoptosis via hyperbaric oxygen; neuroprotective drugs, and anti-apoptotic drugs, such as bromodine (Alphagan, Allergan). Some surgeons advocate using bromodine instilled frequently to theoretically prevent apoptosis in a patient with a total RD. This unproven methodology could help preserve better photoreceptor function during any delay of surgery.

For patients in whom the fovea is attached, a study compared immediate surgery with surgery at three days after detachment, finding no difference in the final outcomes (*Am J Ophthalmol.* 2010;150:201-10).

Bilateral patching is possible. Positioning the patient preop is also an "urban legend" of surgeons to prevent foveal detachment while waiting to get the patient into the OR. Some surgeons advise patients to maintain a position on their side and avoid reading.

Dr. Packo concluded that if the surgery is delayed and the patient has a poor outcome, they may question the delay and the activities. Injecting a bubble is an option that might flatten the macula, although negotiating around the bubble is difficult during buckling. Removing the bubble during vitrectomy can negatively affect the lens. ■

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Dr. Packo has no financial interest in any aspect of this report.

Retinoblastoma survival rates high; secondary cancer a risk

The probability of non-ocular malignancies differ between men, women

By Cheryl Guttman Krader; *Reviewed by Ruth Kleinerman, PhD*

THE 10-YEAR SURVIVAL rate for patients with hereditary retinoblastoma is excellent, but these patients are at increased risk for developing secondary cancers and have elevated mortality compared to age-matched individuals in the general population.

According to analyses of data for retinoblastoma patients in the United States, there are gender-related differences in both the incidence of the different types of second non-ocular malignancies and cause-specific mortality, according to Ruth Kleinerman, PhD, deputy branch chief, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD.

Dr. Kleinerman

"Based on this information, evidence-based guidelines for long-term surveillance and follow-up of retinoblastoma survivors should take gender into account," Dr. Kleinerman said. "International pooling of second cancer data for retinoblastoma survivors will increase the number of cases of second cancers and provide statistical power to further investigate gender disparity in risk with greater precision."

Information on the incidence of second cancers in retinoblastoma survivors and rates of mortality related to the subsequent cancers is available from the National Cancer Institute Long-term Follow-up Study of Retinoblastoma Survivors.

The study includes data on 1,129 patients with hereditary retinoblastoma diagnosed between 1914 through 2006, of whom approximately 50% were still alive in 2016.

According to Dr. Kleinerman, the most common secondary cancers among the hereditary retinoblastoma survivors are bone cancer, soft tissue sarcoma, and melanoma.

Analyses of cause-specific mortality compare the rates of death in the retinoblastoma survivors with those reported for the U.S. population.

The data show that female retinoblastoma survivors have a higher risk of dying of bone cancer, melanoma, and brain tumors and a slightly higher risk of dying of nasal cavity cancers compared with females in the general population.

In addition, rates of death due to lung, bladder, and colon cancer among female retinoblastoma survivors also appear to be higher than females in the general population, whereas male retinoblastoma survivors are at higher risk of dying of pancreatic cancer than males in the general population.

TAKE-HOME

- ***Analyses of cancer incidence and cause-specific mortality patterns for long-term hereditary retinoblastoma survivors shows gender-related differences.***

WHY THE INCREASED RISK?

Genetic susceptibility, treatment, and other factors might contribute to the increased risk of second cancers in patients with hereditary retinoblastoma.

Hereditary retinoblastoma is caused by germline mutations in RB1, and the location of the mutation or the type of the mutation may be involved in the risk of some secondary cancers, including lung, bladder, and brain tumors. In addition, the patients may be carrying mutations in other related pathways.

"RB1 is in the same cell cycle control pathway as CDKN2A, which is a susceptibility gene for familial melanoma and pancreatic cancer," she said.

Host characteristics, such as age and sex, as well as lifestyle and environmental factors, such as smoking history and sun exposure, may also play a role. ■

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This article is adapted from a presentation given by Dr. Kleinerman at the 2018 Ocular Oncology/Pathology Subspecialty Day meeting. Dr. Kleinerman has no relevant financial interests to disclose.

PROGRESSION

(Continued from page 28)

The investigators said they believe that one of these models can be updated and tested with higher risk hospital patients.

Within those three models, there were 11 different types of final predictors, with the duration of diabetes and HbA1c in all three. Two of the models used systolic blood pressure.

"Other predictors included in these three models were presence [of DR], grade of diabetic retinopathy, presence of background diabetic retinopathy in one or both eyes, gender, type of diabetes, age at diagnosis, and total serum cholesterol," the investigators reported.

Based on their findings in this review study, the investigators emphasized the need for a model that can determine patients' individual risk of progression to treatment stage/loss of vision.

This knowledge will allow for more appropriate use of resources and further optimization of services, especially for patients with a higher risk of progression.

"Scanlon et al, Aspelund et al., and the ISDR model seem to be appropriate in terms of contemporary participant data, assessable predictors, and sound methodology, though they do not directly address the outcome of our interest," the investigators concluded. "They need further external validation in diverse high-risk settings before being implemented into clinical practice." ■

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The investigators had no financial interests to disclose related to any aspect of this report.

DREAM Extension study supports primary trial conclusion

Supplementation no better than placebo as results confirm previous research

By Cheryl Guttman Krader; *Reviewed by Penny A. Asbell, MD, MBA*

RESULTS OF THE 12-month Dry Eye Assessment and Management (DREAM) study showed that dietary supplementation with oral omega-3 fatty acids is no better than placebo in relieving signs and symptoms of dry eye disease (DED).

Results from the 12-month DREAM Extension study are consistent with the findings of the primary trial, according to Penny A. Asbell, MD, MBA, study chairperson for the DREAM research group, and Barrett G. Haik Endowed Chair, chairperson and professor of ophthalmology, University of Tennessee Health Science Center, Memphis, TN.

Dr. Asbell

"Many ophthalmologists and optometrists have considered nutritional supplementation with omega-3 helpful for dry eye patients and often added them to other treatment modalities such as artificial tears and topical anti-inflammatory agents," she said.

However, Dr. Asbell explained that the high level evidence for the U.S. population, i.e., results from double-blind randomly selected trials with large sample size, had not been available before DREAM.

"The goal of DREAM was to look at your typical dry eye patient with moderate-to-severe dry eye symptoms despite treatment for dry eye and then add on omega-3 to see if it would help both symptoms and signs," she said.

STUDY CHALLENGES

The study also could prove to be a challenge for both researchers and participants. Dr. Asbell also explained that the study was rigorous and the main results did not show improvement when compared to placebo.

"The DREAM Extension study, adding a second year of treatment, was developed to explore long-term efficacy and safety of omega-3 use for dry eye and to see if any gains over one year of omega-3 treatment continued or were lost when omega-3 was discontinued," she noted. "This withdrawal trial is a unique approach in dry eye disease to better understand long-term treatment and its implications; most industry trials are relatively short weeks or—months, even though in clinical practice we may recommend a treatment for months or even years."

DREAM and the DREAM Extension study are supported by the National Eye Institute.

DREAM enrolled patients who had moderate to severe DED. The patients were to continue any existing DED treatments.

A total of 535 patients were randomly selected 2:1 to double-masked treatment with 3,000 mg omega-3 fatty acids (2,000 mg of eicosapentaenoic acid and 1,000 mg docosahexaenoic acid fish oil concentrate in triglyceride form) or placebo (refined olive oil 5 gm) for one year.

The total daily dose of each study treatment was contained in five soft gelatin capsules, and the omega-3 fatty acid and placebo capsules were identical in size, color, and aroma.

The primary endpoint in DREAM analyzed average change from baseline at six and 12 months in Ocular Surface Disease Index (OSDI) score, and the results showed a significant improvement in both the omega-3 fatty acid and placebo arms with no significant differences between the two study groups.

At baseline, mean OSDI was approximately 45 and it decreased by an average of about 13 points in both groups.

Compliance with the study treatment protocol, changes in DED signs (conjunctival staining, corneal staining, tear break-up time, Schirmer's test score), use of other DED treatments, health-related quality of life, and adverse events were all analyzed as secondary outcomes.

According to the data, there were no statistically significant differences between study groups in any of those measures.

LONG-TERM SUPPLEMENTATION

DREAM Extension, or the withdrawal trial, was part of the original protocol to determine whether continued use of omega-3 for two years increased efficacy and/or if withdrawal (i.e., stopping omega-3) led to a resurgence of dry eye symptoms and/or signs.

"We were not able to enroll as many patients as we needed for the Extension Trial, given the time needed to complete enrollment of the primary DREAM study, but we hoped the data we collected from the Extension trial would shed some light on the effects of long-term use of omega-3 for dry eye disease," Dr. Asbell explained.

Patients were eligible for the DREAM Extension study if they were assigned to the omega-3 fatty acid group in the primary trial and completed the 12-month study visit.

A total of 43 patients participated in the DREAM Extension study, which was also double-masked. Patients were randomly selected 1:1 to continue omega-3 fatty acids treatment or were switched to placebo (olive oil 5 gm).

PATIENTS SIMILAR

Patients in the extension trial were similar to those who had been enrolled initially in DREAM, and the two treatment groups in DREAM Extension were also similar to each other in their baseline characteristics at the start of the extension phase study.

Changes in DED symptoms assessed with the OSDI were analyzed by researchers as the primary outcome measure.

At the end of the DREAM Extension study, the OSDI was increased slightly in both groups, but the changes were not statistically significant, and there was no statistically significant difference between study groups.

In secondary outcome analyses, researchers found that there were no statistically significant differences within or between study groups in changes in signs of DED over time, including conjunctival staining, corneal staining, tear break-up time, or Schirmer test score.

Adverse event rates were also similar among patients who were taking omega-3 fatty acids and those receiving the placebo. ■

TAKE-HOME

- ***Results from a 12-month extension of a randomized, placebo-controlled, double-masked trial are consistent with the primary trial that did not support a beneficial effect of omega-3 fatty acid supplementation on dry eye disease.***

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This article is based on a poster presented at the 2019 annual meeting of the Association for Research in Vision and Ophthalmology. The DREAM study was published in 2018 [Dry Eye Assessment and Management Study Research Group. N Engl J Med. 2018;378(18):1681-1690].

Dr. Asbell receives research grants and had been a consultant to companies that market treatments for dry eye disease. She has not received any funding from companies related to omega-3.

Photoreceptor replacement cells enter therapeutic space

Ganglion, bipolar cells increase options for patients with late-stage retinal disease

By Lynda Charters; *Reviewed by Edwin M. Stone, MD, PhD*

Human retinal engineering is a rapidly growing field, albeit an expensive one.

"Cost containment is becoming increasing important in medicine because without some type of substantial governmental or actuarial wealth redistribution, the vast majority of people in the United States will not be able to afford the life-changing treatments that science is developing," said Edwin M. Stone, MD, PhD.

GOAL OF STEM CELL TRANSPLANTATION

The goal of this technology is durable restoration of useful vision in patients with advanced stages of retinal degeneration. These diseases range from very common age-related macular degeneration [AMD], which affects millions of patients to the unusual forms of retinitis pigmentosa [RP], which affect only a few patients at any one time.

Dr. Stone

"What unifies these conditions is the selective loss of the outer retina," said Dr. Stone, professor of ophthalmology, and the director of the University of Iowa Institute for Vision Research, Iowa City, IA.

The key players involved with vision in the retina are the photoreceptors, bipolar cells, and ganglion cells. In AMD and RP, the photoreceptors are lost, but the ganglion and bipolar cells remain over decades even in the presence of no light perception vision, he explained.

Recognition of this has set the stage for transplantation of a graft into the subretinal space to replace the photoreceptors.

Dr. Stone noted that this has already been achieved in a few different animal models. In a blind mouse model, increased electroretinographic activity was observed with increasing doses of injected cells.

HOW IT WORKS

When considering this type of intervention in humans, Dr. Stone pointed out the need for two strategic decisions: first, whether to use autologous cells or cells from another individual and, second, the type of injection, i.e., a bolus injection or a polymer supported sheet.

In Dr. Stone's group, the investigators have opted to use autologous cells that are supported by a polymer. They reached this decision, he explained, because of the increasing evidence that retinal allografts are associated with a robust immune response even when the recipient has a normal retina before transplantation. Autologous grafts have the added advantage that they will minimize the need for expensive, somewhat toxic, life-long immunosuppression.

"If new retinal cells can be derived from the patient for whom they are intended, those cells would be the best possible immunologic match and require the least immunomodulation," he explained.

Induced pluripotent stem cells (iPSCs) can be differentiated into photoreceptor precursor cells for autologous transplantation. However, the downside to this strategy is that in a patient with RP they still contain the mutations that caused the disease.

To counteract this, the CRISPR/CAS9 genome editing system can correct the mutations in the iPSCs before differentiating them into the retinal cells, Dr. Stone explained.

PHOTORECEPTOR MECHANISIMS

Dr. Stone explained the procedure to create patient-derived photoreceptor precursor cells. The first step is obtaining a skin biopsy in order to establish a fibroblast culture. These fibroblasts are then treated with four pluripotency factors that erase the cells differentiated state and then turn them into iPSCs. When cultured with additional growth factors that drive core brain development, the cells begin developing structures that resemble eye cups after about 30 days. The eye cups then are removed and cultured with growth factors that induce further retinal development.

"In a matter of weeks, transplantable photoreceptor precursor cells are available," Dr. Stone stated.

However, the vast majority of the cells, i.e., 90%, will die if they are just injected as an unsupported bolus under the retina. This is the stage at which the polymer support, which can be created using a three-dimensional printer, comes into play. The polymer support increases the cellular survival rate. The printer can print dissolvable biopolymer scaffolds at a subcellular scale, he explained.

The scaffold has three-dimensional channels that are about 10 microns in diameter. In the rat, optical coherence tomography showed an intact retina draped over a graft that was slowly dissolving 6 months after implantation.

The first trial performed in completely blind patients will involve implantation of a 5-mm circular graft containing about 500,000 photoreceptor precursor cells. In order for this technology to be affordable for most patients, many of the steps required to handle the cells will be performed by robots.

To make this technology available throughout the country, multiple regional stem cell facilities connected to surgical suites will need to be established because the grafts are living tissue that cannot be transported long distances.

"Photoreceptor replacement therapy is steadily moving closer to the clinic," Dr. Stone concluded. "With the use of patient-derived cells, we can reduce the need for expensive long-term immunosuppression. Robots will help reduce manufacturing costs, which will increase access to these treatments for our patients." ■

TAKE-HOME

- ***Treating late-stage retinal disease with induced pluripotent stem cells is on the clinical horizon.***

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Dr. Stone has no financial interest in any aspect of this report.

Drugs offer activation combination of Tie2 pathway in DR, DME

May provide better anatomic improvement, decreased DR severity scores

By Lynda Charters; *Reviewed by Peter K. Kaiser, MD*

TIE2, A TYROSINE kinase receptor, has become an important focus of research, and when combined with vascular endothelial growth factor (VEGF) therapy the two may provide better outcomes for patients with diabetic retinopathy (DR) and diabetic macular edema (DME) than with VEGF drugs alone.

HOW IT WORKS

During gestation, the Tie pathway is key to the development of the ocular and vascular structures and its absence is lethal to normal development, according to Peter K. Kaiser, MD.

Dr. Kaiser

Dr. Kaiser is the Chaney Family Endowed Chair in Ophthalmology Research, and professor of ophthalmology, Cole Eye Institute, Cleveland Clinic Lerner College of Medicine, Cleveland.

In adults, the Tie pathway is the "gatekeeper" of vascular quiescence, he noted. It regulates blood and vascular homeostasis, inflammation, and pathologic angiogenesis and has a key role in cancer and diabetes.

When things are working normally, the key Tie2 ligand, angiopoietin 1 (Ang1), binds and activates Tie2, which promotes the integrity of blood vessels. Dr. Kaiser said this is done by forming into high order oligomers that produces clustering of the Tie2 receptor required for activation.

In contrast to Ang1, Ang2 is a weak agonist that is released in the presence of hypoxia, inflammation, and VEGF. Ang2 is mainly found in dimer form and does not cause Tie2 receptor clustering and thus no receptor activation. This leads to vascular leakage, inflammation, and vascular instability.

The Tie receptors are found largely on endothelial cells that provide the microenvironment in which activation can occur.

"The Tie1 receptor is an orphan receptor that regulates Tie2 receptor trafficking and is necessary for full Tie2 activation," Dr. Kaiser said.

Activation (phosphorylation) of Tie2 is instrumental in a number of essential functions, including enhanced endothelial cell survival, decreased leakage, and anti-inflammatory effects. On the flip side of the coin, deactivation (dephosphorylation) of Tie2, results from the activity of Ang2 that prevents clustering of the Tie2 receptors, causes pericyte detachment from vessels, increased vascular leakage, and inflammation.

Another player in this cascade is vascular endothelial-protein tyrosine phosphatase (VE-PTP), rheostat that modulates the effect of Ang2 on Tie2, Dr. Kaiser explained.

VE-PTP dephosphorylates the Tie2 receptor and mediates cross-talk with the VEGF receptor 2, which shows how the tyrosine kinase pathways are interrelated. It works independent of Ang1 and Ang2.

EFFECTS OF ANG AND TIE IN RETINAL DISEASE

Ang1 is protective against vascular dysfunction in diabetes, but this effect is counteracted by the presence of dyslipidemia and hyperglycemia. Hyperglycemia also elevates the levels of Ang2, which is associated with the increased severity of DR.

In the vitreous, Ang2 levels are elevated in patients with proliferative DR and Ang1 levels decrease. As a result, activating Tie2 in patients with diabetes is a goal.

PHARMACEUTICAL INTERVENTION

The first drug tried to achieve this goal was nesvacumab (REGN910, Regeneron Pharmaceuticals/Bayer), an experimental antibody to Ang2 that leads to activation of Tie2.

The phase II RUBY clinical study showed that the Ang 2 antibody combined with intravitreal injection of aflibercept (Eylea, Regeneron Pharmaceuticals) resulted in an increase in fluid resolution when compared with aflibercept alone (90.4% versus 74.0%, $p=0044$) in patients with DME.

This outcome was also true for the combination therapy in patients with DR.

"The combination of Ang2 inhibitor and aflibercept led to decreased severity of DR, and the reduction was greater in association with higher Ang2 levels in patients with severe and proliferative disease," Dr. Kaiser said.

A second drug, faricimab (Genentech Inc./Roche), was found in the phase 2 Boulevard Study to activate Tie2 and block VEGF in DME. Again, combining Ang2 inhibition and anti-VEGF therapy resulted in better fluid control and better visual outcomes than ranibizumab alone. It is particularly true in patients who had received previous anti-VEGF treatment. The study also showed improved DR severity scores compared with anti-VEGF therapy alone, Dr. Kaiser emphasized.

A third drug, AKB-9778 (Aerpio Pharmaceuticals), is a small-molecule inhibitor of VE-PTP. This formulation activates Tie2 regardless of the levels of Ang1 or Ang2, Dr. Kaiser explained. This activity is in contrast to the activity of nesvacumab that, when administered alone, did not significantly activate Tie2 in human endothelial cells.

The TIME2 phase IIa study of AKB-9778 also showed that the combination of the Tie2 activator and ranibizumab (Lucentis, Genentech Inc.) showed significant ($p=.008$) decreases in the central retinal thickness and the diabetic retinopathy severity compared with either of the drugs alone. Interestingly, AKB-9778 is administered by subcutaneous injection.

The results of elevated Ang2 levels are substantial: improved proteinuria, peripheral neuropathy, erectile dysfunction, myocardial function, and wound healing.

TAKE-HOME

- ***Tie2 activators combined with anti-vascular endothelial growth factor therapy translate to improved anatomic function and decreased diabetic retinopathy severity scores.***

CONCLUSION

"Diabetic studies with three different Tie2 activators reported significantly improved anatomic measures and diabetic retinopathy severity scores compared with anti-VEGF alone," Dr. Kaiser concluded. "As a result of the unique mode of action and interplay between VEGF and the Tie2 pathways, combining these modalities may achieve even better treatment outcomes in our diabetic patients." ■

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Dr. Kaiser is a consultant to Aerpio Pharmaceuticals, Allegro Ophthalmics, Bayer, Regeneron, and SciFluor.

Automated patient reminder system could boost patient compliance

EHR-linked system explored as strategy for improving glaucoma medication adherence

By Cheryl Guttman Krader

FINDINGS FROM A prospective study conducted at the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, demonstrate the feasibility of creating an automated reminder system for glaucoma medications using the electronic health record (EHR) and show that such a system is generally well-received by patients.

The investigators noted that additional longitudinal studies are needed to determine the clinical relevance of the portal-linked system for improving medication adherence and glaucoma outcomes.

Reported in the March 2019 issue of *JAMA Ophthalmology*,[1] the study recruited patients from the Wilmer Eye Institute glaucoma clinic who were being treated with IOP-lowering medications.

Patients were approached from April 2017 to January 2018 and asked about their willingness to use a computer-based system to configure medication reminders.

Those who agreed to enter the study were interviewed to assess medication adherence, current use of reminders, and the likelihood they would use electronic health record (EHR)-linked reminders.

Participants were asked to set up the reminders themselves, or with the assistance of a family member. Help from a research coordinator was also available if preferred.

The reminders were voice- or text-based. Text-based messages also asked patients to respond within 30 minutes, and if patients failed to respond, the system delivered a second message encouraging them to respond. Three months after entering the study, participants were contacted by telephone and interviewed again for feedback about their experience with the system.

TAKE-HOME

- ***Poor adherence with glaucoma medications is a recognized problem, and an automated reminder system could increase patient compliance rates.***

OUTCOMES

The recruitment effort showed reasonable patient willingness to use the system. Of 147 patients approached about entering the study, 100 (68%) agreed to participate. Those participants had a mean age of 65 years, included 54 men and 46 women, represented a heterogeneous racial mix (51% whites, 33% blacks, and 13% Asians), and had been on glaucoma medications for an average of 11.3 years.

Compared with patients who declined to participate, those who were willing were similar with respect to most baseline characteristics.

Patients who participated had a lower self-reported medication adherence rate than those who were unwilling (91% versus 97%). However, rating of risk for poor adherence (defined as ≥50% probability of nonadherence) using a previously validated scoring system showed that the percentage of patients rated at high risk for poor adherence was slightly lower within the group that agreed to participate than in the group that declined (9% versus 11%).

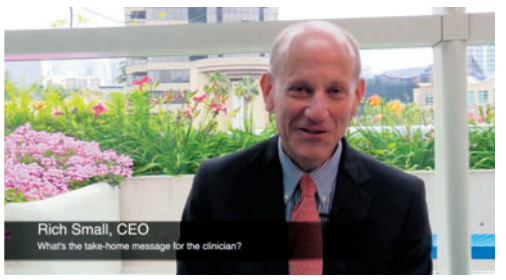
Overall, 94 of the 100 patients who agreed to participate configured the reminders; 72 patients requested help with the configuration, but those who set it up themselves found it was easy to use. The majority of patients chose to receive text messages (67%), and about one-fourth preferred voice message reminders, while the remainder wanted email notification. The majority of patients (69%) were using more than one topical medication, but two-thirds of patients chose to configure a reminder for just one medication rather than for all of the drops they were using.

Of the 94 patients who configured the reminders, 89 (95%) completed the three-month follow-up visit.

Data from the follow-up interviews showed that approximately three-fourths of the patients found the reminders to be useful, while 15% were neutral about their value, and 11% stated they were not useful. However, only 47% of patients said that they were very likely or likely to continue using the reminders, while 11% were neutral, and 42% said they were unlikely or very unlikely to continue.

Overall, **94 of the 100 patients** who agreed to participate configured the reminders; **72 patients** requested help with the configuration, but those who set it up themselves found it was easy to use. The majority of patients chose to receive text messages (**67%**), and about **one-fourth** preferred voice message reminders, while the remainder wanted email notification. The majority of patients (**69%**) were using more than one topical medication, but **two-thirds of patients** chose to configure a reminder for just one medication rather than for all of the drops they were using.

ONLINE EXCLUSIVE



VIDEO Rich Small, CPA, CEO, of Neurotech Pharmaceuticals, Inc., shares what's in the pipeline for new glaucoma treatments.
Watch his interview at **https://bit.ly/2FANNgP**

RESEARCH RATIONALE

Patients' nonadherence with glaucoma medications is a recognized problem. Previous research has found that forgetting to use medications is a leading cause of poor adherence and that automated telecommunication-based reminders can improve adherence.

Varadaraj and colleagues noted that broad adoption of automated reminders has been hampered by the difficulty linking them to the medications patients are using. They stated that the EHR offered an opportunity to address this issue and would have the advantage of allowing clinician oversight to ensure application to currently used medications. ■

REFERENCE

1. Varadaraj V, et al. Association of an electronic health record-linked glaucoma medical reminder with patient satisfaction. *JAMA Ophthalmol*. 2019;137(3):240-245.

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Flying solo poses challenges, flexibility and support vital

Operating a small practice may require physicians to wear many hats

By Nancy Groves; *Reviewed by Lisa M. Nijm, MD, JD*

RUNNING A SOLO or small practice today can be a challenge, and the question is whether it is sustainable.

Judging from comments by experts, the short-term answer might be "no."

But not so fast, according to Lisa M. Nijm, MD, JD, who five years ago founded her own solo practice, Warrenville EyeCare and Lasik, Warrenville, IL. She is also associate professor of ophthalmology, University of Illinois Eye and Ear Infirmary.

For one thing, young ophthalmologists deciding on their career direction have a distinct advantage over colleagues in most other specialties.

"We are one of the few specialties in medicine that has the luxury of not being connected to a hospital in most cases, and therefore we have more ability to pursue a solo practice," Dr. Nijm said. "If you want to build your own business and you have the drive and entrepreneurial spirit to hang you own shingle, you can do it. Studies show a decreased rate of burnout and greater physician satisfaction in solo or small group practices."

Dr. Nijm suggests that the first step when considering a solo practice is to do some serious soul searching. Physicians should consider what they are looking for in a practice day-to-day and whether this ideal is more likely to be found in an academic or private practice, a solo or group setting.

"The more that you self-reflect and develop a clearer picture of what you're looking for, the better prepared you will be to evaluate if your expectations match those of the practice settings that you're considering," she said.

Dr. Nijm followed this advice when deciding to open her practice after having worked in both a small, ophthalmology-only group and a large multispecialty clinic. She was motivated by her desire to develop deeper relationships with her patients and maintain autonomy and independence while having the flexibility to adopt new technologies when she felt that it would best serve her patients.

She outlined her formula for success in solo practice.

"Imagine yourself like Han Solo in the Star Wars movies," she said.

Similar to the personality and actions this character displayed in the original trilogy, she recommends:

- **Being friendly, adaptable, and action-oriented**
- **Planning ahead**
- **Building a squad or team with shared goals**
- **Recognizing challenges**
- **Using various resources available to you to help establish your practice**

Dr. Nijm suggested that a solo practitioner would ideally have an amicable personality, which would allow them to easily talk with patients and maintain good relationships with staff members. Other desirable traits would include the ability to adjust to new technology and regulatory requirements. As a business owner, they must possess the willingness to take action when problems arise.

Physicians who fit this description also must focus on the concept of planning ahead.

"It takes a lot longer than you may anticipate to set up a solo practice," Dr. Nijm said.

Before seeing the first patient, physicians need to create a business plan, understand the community they are working in, and be realistic about how long it will take to be accepted on insurance panels and obtain hospital credentials.

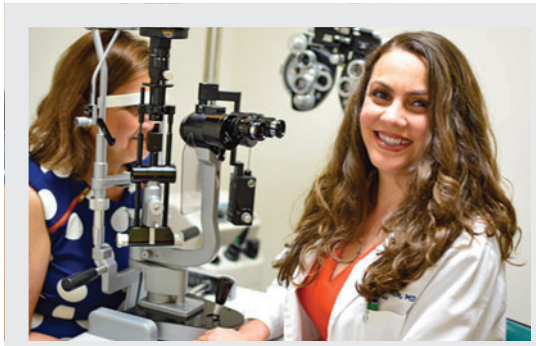
Often, there is a lag time between opening a practice and receiving steady reimbursements. Therefore, a major consideration is obtaining the necessary funding ahead of time to purchase equipment, hire staff, and float a functioning practice for anywhere from three to six months.

TAKE-HOME

- ***Ophthalmologists operating a small practice are looking for better patient relationships and independence.***

'STRIKE BACK' AGAINST CHALLENGES

Then, just as the cinematic "rogue hero" Han Solo was constantly doing battle with Darth Vader and other villains, solo practitioners will confront their own particular challenges: insurance companies and Medicare, billing and coding—not something physicians should simply leave to their staff, Dr. Nijm emphasized—as well as government compliance requirements and human resources.



Solo practitioners should have amicable personalities, so they are able to easily talk with patients and maintain good relationships with fellow staffers. *(Photo courtesy of Lisa M. Nijm, MD, JD)*

Again, like Han Solo, who had help from an assortment of partners as he crisscrossed a galaxy far, far away, solo physicians are leaders who must build a strong and compassionate supporting team, united around a core theme.

"You want to send the message from the beginning that you put the patient first," Dr. Nijm said. "When you put the patient first, everything else falls into place."

Resources such as the IRIS registry (Intelligent Research in Sight) can be extremely helpful to solo practitioners, she added, and advised doctors just starting out on their own to spend time interacting with other physicians in the community, which can result not only in a useful business network but lasting friendships.

"I'm confident that if you follow these steps with the goal of providing the best care for our patients, the next big thing will be the return of the solo practice," Dr. Nijm concluded. ■

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This article was adapted from Dr. Nijm's presentation at the 2018 meeting of the American Academy of Ophthalmology. Dr. Nijm did not report any relevant financial relationships.

Five-step leadership system supports patient workflow, staff efficiency

System works well to get office employees moving in the right direction

By David Hutton; *Reviewed by Derek A. Preece, MBA*

FOR ANY PRACTICE striving for greatness, its fortunes are closely tied to its people. As a result, it is imperative for management to put staff in the best position to succeed. Derek A. Preece, MBA, discussed five ways to manage a successful practice. The system works well to get employees moving in the right direction. It also can be effective in handling difficult employee situations.

Preece

Virtually every practice has systems in place for checking patients in, and working up patients, as well as for billing and collections.

"When I ask practice administrators if they have a system for leading their staff, they often give me a blank look," he said. "Practices have systems for everything else, but almost never do they have a system for managing staff."

A "system" is a step-by-step method for accomplishing work. Systems help us make sure that we are doing everything we need to do to be successful. If there is a problem, the system can be reviewed to determine where a breakdown is occurring. Consistency can be developed.

"A system for leadership will help you lead your employees appropriately," Preece noted. "It helps define what your responsibility is as an administrator and it helps to limit that responsibility."

Here is the five-step system that Preece cited:

1 PROVIDE THE TOOLS

While virtually every office provides computers, equipment and phones, Preece noted that improvements can be made in forms and processes, improving communications between departments.

2 PROVIDE THE TRAINING

Training is key because it helps physicians or practice administrators reveal their expectations to employees.

"You let them know what you expect them to get out of the training," Preece explained.

Training concepts such as "spaced repetition" can be used to help staff get a handle on new tasks. Spaced repetition incorporates training that is repeated over several weeks or months to provide employees time to absorb the new processes and put them into action.

Managers should model appropriate interactions between staff and patients to set an example. Most practices find that they need to teach people skills to their staff in addition to the business tasks they are required to perform.

3 SET GOALS

Setting goals, Preece explained, is done to give employees direction and help them measure progress. A lack of goals can lead to frustration among staff. He said employees can be tasked with setting their own goals.

"You can't make them accountable unless you have written goals," he said. "If you let the employees set their own goals, they will usually be pretty ambitious."

The physician or administrator can approve the goals and offer guidance. Allowing the employees to set the goals offers a sense of accomplishment.

4 BE A RESOURCE

A key step, according to Preece, is becoming a resource for the staff.

"Employees need to feel they can come to you," he said. "You have to listen, be open-minded and be trustworthy."

Overreaction to a problem could shut off the flow of communication, so make sure responses to bad news are measured and appropriate.

As a resource, physicians or administrators should offer support, and training. They should not take over their work.

"You do not want to take the monkey on your back," Preece explained. "If employees find that when they come to you with a difficult task, you reward them by relieving them of that responsibility, you are incentivizing them to do that."

5 HOLD STAFF ACCOUNTABLE

The final step is holding employees accountable. While deadlines are set for goals, moving forward is just as important as accomplishing the goals.

"The deadline is needed to make sure we move toward accomplishing goals," Preece said. "But don't get stuck on whether specific deadlines are met or not, since most timelines are set without perfect knowledge of future events. It is more important to focus on how much progress is made."

Employees can chart progress toward their goals in writing. This creates a paper trail that physicians can review, and a higher level of accountability.

"Provide feedback to offer correction when necessary and commendation whenever possible," Preece added. "I have found during more than 40 years of managing people, if I am truly thankful for the work they do, they will bend over backwards to accomplish what needs to be done."

There are five steps to employee responsibility for staff members:

1. **Use the tools that are provided**
2. **Apply the training they receive**
3. **Set and accomplish goals**
4. **Ask for help when needed**
5. **Be accountable for progress towards goals**

With the steps, administrators and physicians will be able to weed out underperforming employees. Poor performing employees do not like to set goals or be held accountable. They will often decide to leave rather than face the pressure of performing well. The system also can determine if an employee is in the wrong position.

The five step leadership system helps to keep staff members happy and engaged.

"As the leader of the practice, if you apply the five step leadership system, you will have motivated employees," Preece concluded. "You also will achieve practice success as you get your entire staff aligned with your objectives through setting and accomplishing their own goals." ■

TAKE-HOME

- ***The five-step leadership system can work well to get your employees moving in the right direction. It can also be effective in handling difficult employee situations.***

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This article was adapted from Preece's presentation at the American Academy of Ophthalmic Executives annual meeting. He has no financial interests or relationships to disclose. Allergan is a client of BSM Consulting.

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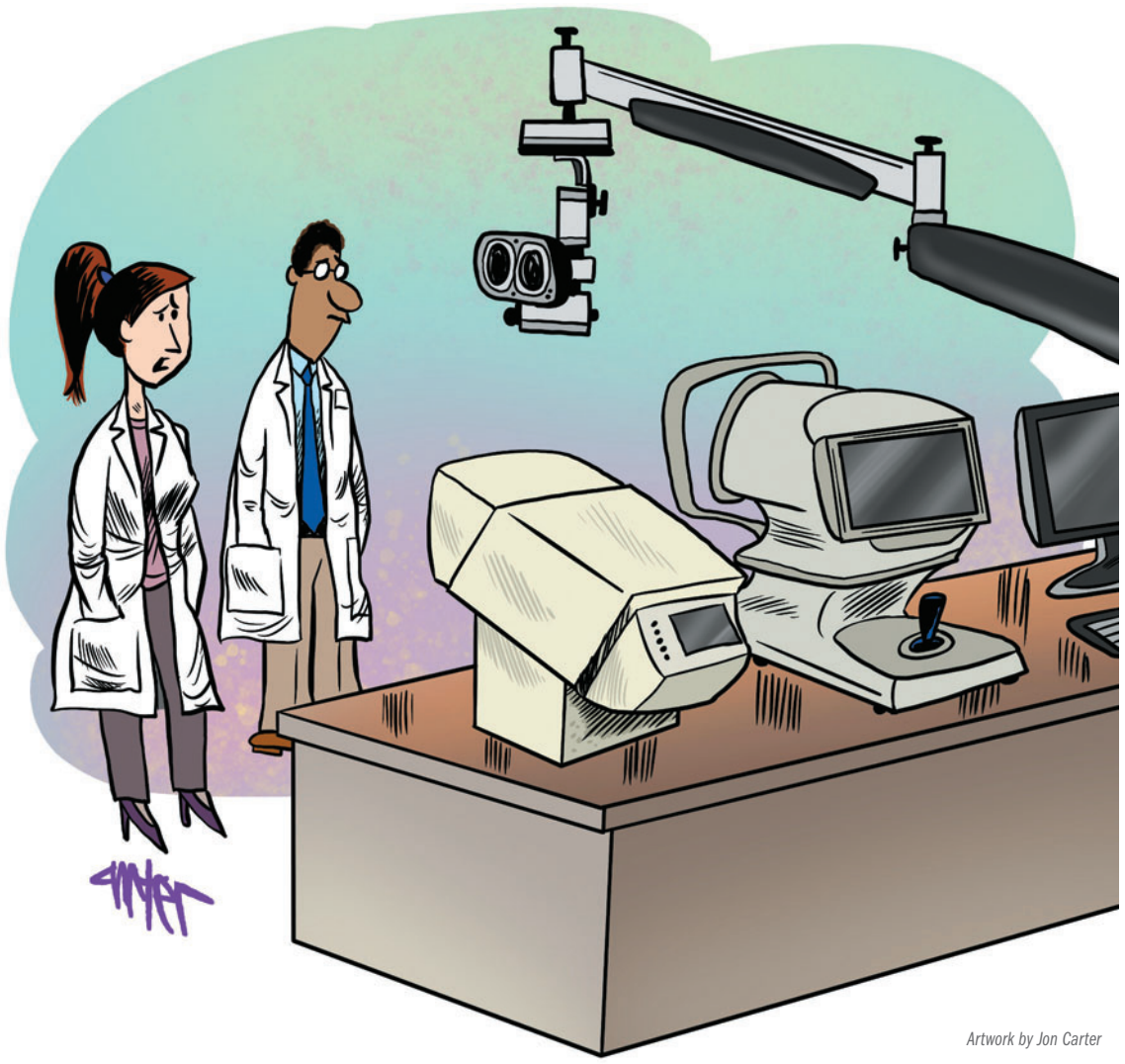

Artwork by Jon Carter

"These are all great, but the best equipment we ever bought for office morale was a new coffee maker."

in case you missed it

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Tonometry can offer tool in CME prevention PAGE 12

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oxervate™
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Brief Summary of Safety

Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

ADVERSE REACTIONS

Clinical Studies Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [*see Clinical Studies (14)*].

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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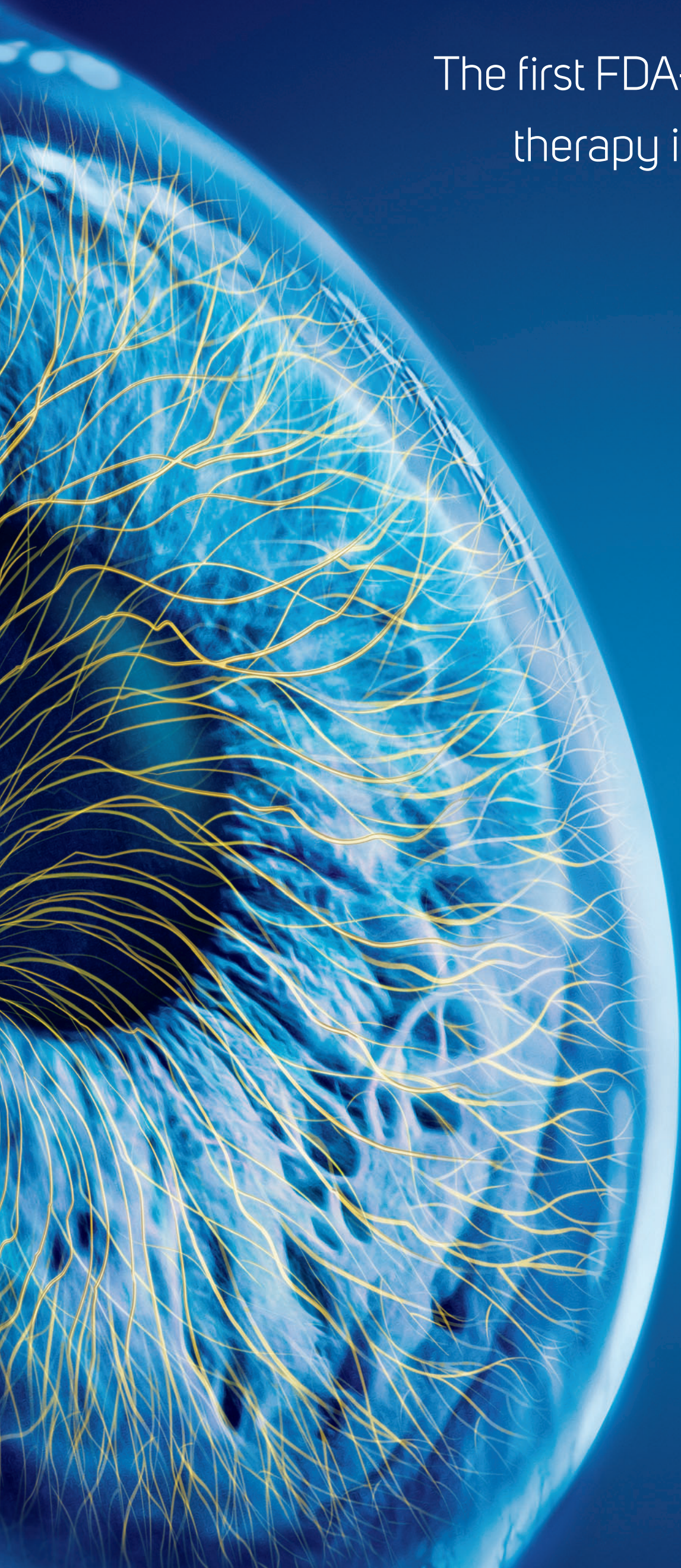

The first FDA-approved pharmacologic therapy indicated for the treatment of neurotrophic keratitis[1,2]

oxervate™

(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Learn more at Oxervate.com/HCP

Important Safety Information

WARNINGS AND PRECAUTIONS

Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

ADVERSE REACTIONS

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears (1%-10% of patients).

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and full Prescribing Information on Oxervate.com/HCP.

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References: 1. OXERVATE (cenegermin-bkbj) full prescribing information. Dompé. May 2019. **2.** FDA approves first drug for neurotrophic keratitis, a rare eye disease [FDA news release]. August 22, 2018.

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